

STUDIES ON THE STRUCTURE AND SYNTHESIS
OF THE IPECAC ALKALOIDS

by

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INTRODUCTION

The alkaloid emetine was used more than a century ago in crude form as the chief active constituent of the drug Ipecac, which was extracted from certain tropical roots. As the name emetine implies, it has found use as an emetic and as an expectorant, but it is best known as a remedy for amoebic dysentery, due to its toxic action on Entamoeba histolytica.

The first isolation of the crude alkaloid in 1817 is credited to Pelletier and Magendie (1), but it was not until 1894 that Paul and Cownley (2) separated emetine itself in pure form. Four closely related alkaloids occur along with emetine in Ipecac. These are present in much smaller quantities and are pharmacologically less effective than emetine. Paul and Cownley also isolated pure samples of cepheline and psychotrine. Later, the other two members of the family, O-methylpsychotrine and emetamine, both occurring in very small proportions in Ipecac, were isolated by Pyman (3).

The usefulness of emetine is limited by its emetic action and toxicity. As a result it has been replaced to a great degree by synthetic amoebicides. In recent years, however, there has developed a widespread interest in emetine, but principally from the chemical rather than pharmaceutical standpoint. The structures of emetine and the other members

of this family of alkaloids have been the subject of intermittent investigation by numerous researchers for several decades, but it was not until 1949 that the complete structure of the molecule was quite clearly established by Pailer and co-workers (4).

At present several groups of researchers are known to be working on the total synthesis of emetine, and the synthesis of one of the racemic forms of emetine has been claimed by Evstigneeva and co-workers (5). Their report is not supported by any experimental details, however, and is therefore somewhat valueless.

The primary purpose of the work described in this thesis was to accomplish a total synthesis of emetine or possibly one or more of its stereoisomers. The presence of four dissimilar asymmetric carbon atoms in emetine allows for 16 possible isomers. Although this primary aim was not accomplished, the various methods of attack on the problem have produced some information which may be useful to others engaged in this type of synthetic work. In addition, one definite contribution has been made to the proof of structure of the emetine family of alkaloids. In investigating the structure of O-methylpsychotrine, Karrer, Eugster, and Ruttner (6) obtained N-benzoyl-corydaldine as a degradation product, but identified it only by the elemental analysis. This compound has now been synthesized and found to be identical with the product obtained by the above-mentioned workers.

Since the main object of this work was the synthesis of emetine, several minor problems which developed during the course of the research, such as the mechanisms of unexpected reactions and the identity of certain by-products obtained in low yields, were by-passed. When planned syntheses gave unexpected results or extremely low yields, they were usually abandoned in favor of a new approach.

BACKGROUND AND HISTORICAL REVIEW

A. Determination of Structure of the Ipecac Alkaloids

The nature of some of the functional groups of emetine was known before the turn of the century. Paul and Cownley (2), at the time of their isolation of emetine in 1894, performed analyses to determine the percentage composition of the elements. Their proposed empirical formula was later proven incorrect, however, and other workers during succeeding years also proposed a variety of erroneous empirical formulas.

The first important contribution towards establishing the structure of emetine was reported by Carr and Pyman (7) in 1914. By carefully studying earlier reported work, much of it contradictory, and supplementing this with accurate laboratory analyses of their own, they arrived at the correct molecular formulas for emetine, cepheline, and psychotrine. In addition they identified all of the main functional groups.

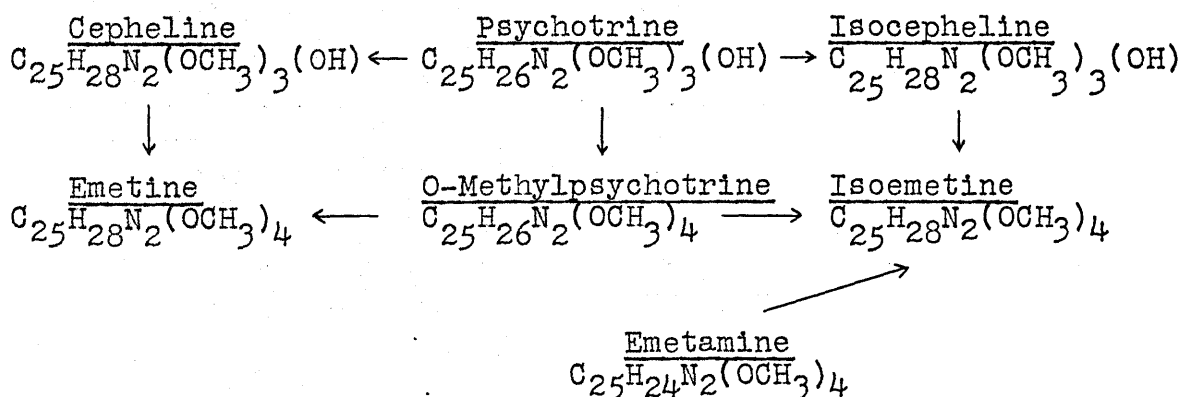
Spurred on by the need for agents to combat amoebic dysentery among the allied armed forces, Pyman and co-workers continued intensive research on the Ipecac alkaloids, and in 1917 (3) reported the isolation and characterization of O-methylpsychotrine and emetamine, thereby completing the family of Ipecac alkaloids.

The table below gives the molecular formulas of each of these alkaloids and the average abundance of each as found

in Brazilian Ipecac.

Name	Molecular Formula	Approximate Percent of Total (8)
Emetine	$C_{29}H_{40}N_2O_4$	71
Cepheline	$C_{28}H_{38}N_2O_4$	26
Psychotrine	$C_{28}H_{36}N_2O_4$	2
O-Methylpsychotrine	$C_{29}H_{38}N_2O_4$	1
Emetamine	$C_{29}H_{36}N_2O_4$	0.2

By 1917 considerable information concerning the nature of all the related alkaloids had been obtained. Some of the work was originally reported by other researchers, but Pyman and co-workers were responsible for investigating the various claims, verifying some, disproving others, and arriving at the following correct functional relationships among the alkaloids and some of their diastereoisomers (horizontal arrows indicate hydrogenation, vertical ones, methylation).



It was also shown by Pyman that both nitrogen atoms in emetamine were tertiary, while the other four alkaloids

contained one secondary and one tertiary nitrogen. Since emetamine could not be reduced to O-methylpsychotrine, Pyman thought that the double bond in the latter was not the same as either of those reduced when emetamine was converted to isoemetine. This conclusion can be questioned in the light of present knowledge.

Most of the elucidation of the structure of emetine was accomplished by two general types of reactions common in alkaloid chemistry: (1) oxidation; (2) methylation followed by degradations of the Hofmann type. Workers contributing to this phase of the work prior to the time of Pailer's final proof of structure included: Keller (9, 10), Windaus and Hermanns (11), Karrer (12), Pyman (3, 7, 13, 14, 15), Spaeth and Leithe (16), Ahl and Reichstein (17).

The principal discoveries of this type leading to the partial establishment of the structure of emetine included the following:

1. On the basis of exhaustive methylation studies it was determined that the secondary nitrogen atom of emetine belonged to one ring, and that the tertiary nitrogen atom was a common member of two rings.

2. By oxidation studies, it was established that the molecule contained at least one 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline group, and probably two such groups.

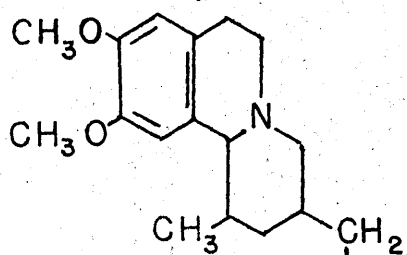
In 1927, three structures for emetine were proposed by Brindley and Pyman (15) (I), Staub (18) (II), and Spaeth and

Leithe (16) (III). All three were partly speculative in nature, with the Spaeth and Leithe formula being the closest to representing actual knowledge at that time.

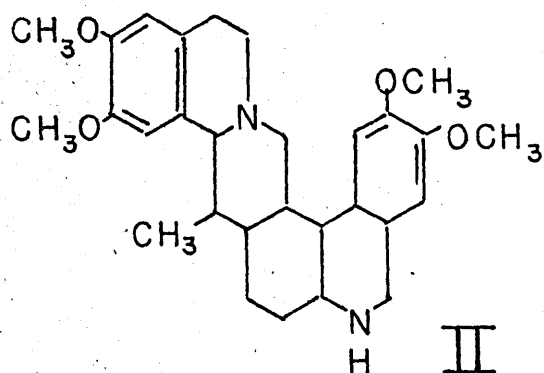
The main arguments for the structure of the middle portion of the molecule, as depicted by Brindley and Pyman and by Staub, were based on the oxidation of emetine to the rubremetinium cation, $C_{29}H_{33}N_2O_4^{\oplus}$, by means of mild oxidizing agents. Since the structure of the cation had not been conclusively determined, however, these formulas were purely speculative. Brindley and Pyman were also partially influenced by R. Robinson, who, on the basis of biogenetic synthesis theory, had suggested a structure similar to I, but with a different location of the side chain methyl group.

Most of the literature on emetine has been concentrated during three periods: 1913-18; 1927; 1948 to the present. To be sure, there were a few scattered publications before the first period and between the periods, but the vast majority of emetine literature is concentrated in these three periods. The major developments of the first two periods, dominated by Pyman and co-workers, have already been described. Thus far, the highlight of the "modern" period is the complete proof of structure by Pailer and co-workers, which led to the correct emetine structure, IV.

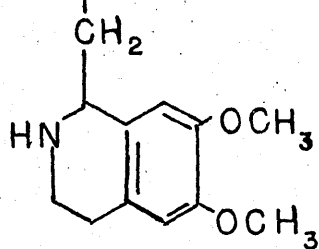
Pailer, et al, employed the general methods of methylation and Hofmann degradation, as well as oxidation and reduction, followed by the synthesis of two of the degradation



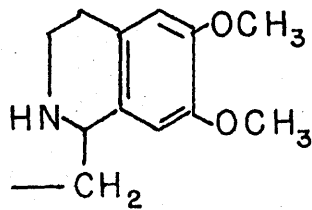
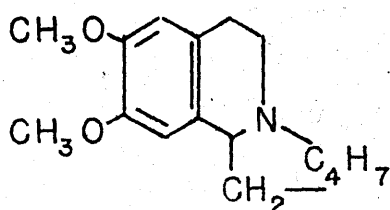
I



II

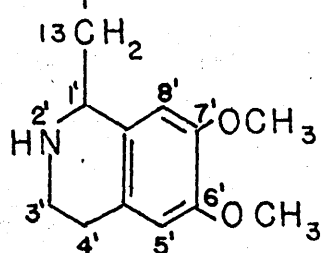
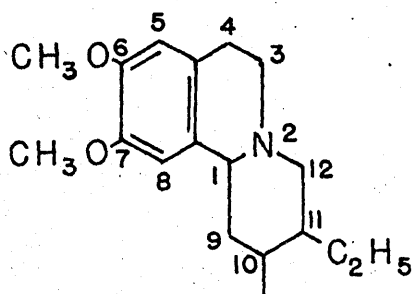


III



IV

EMETINE



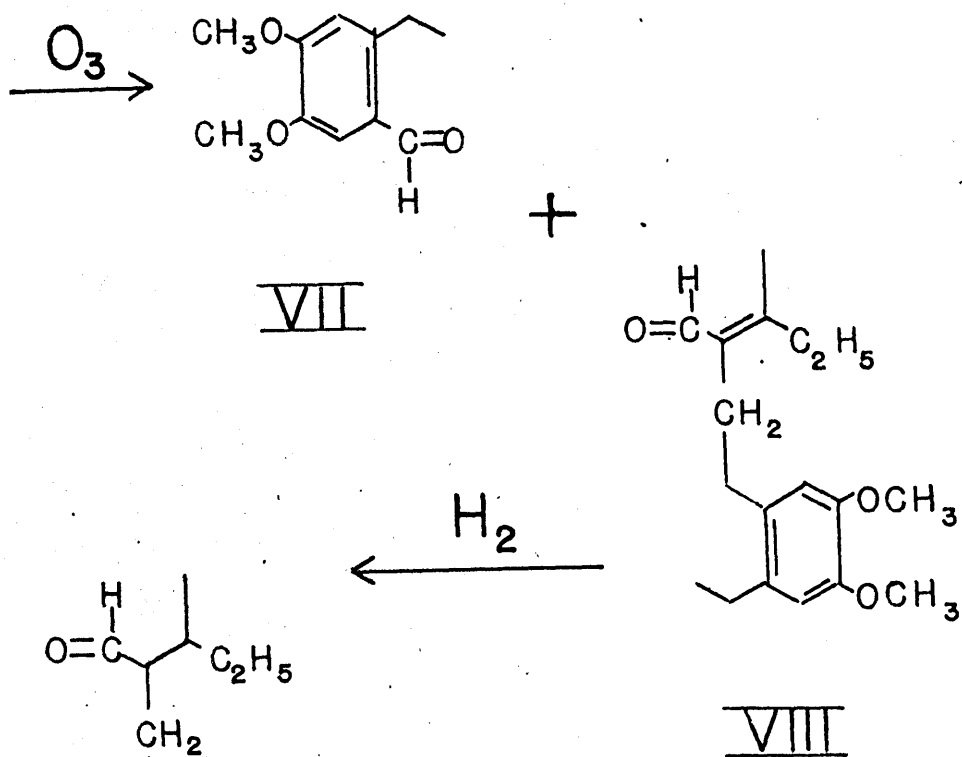
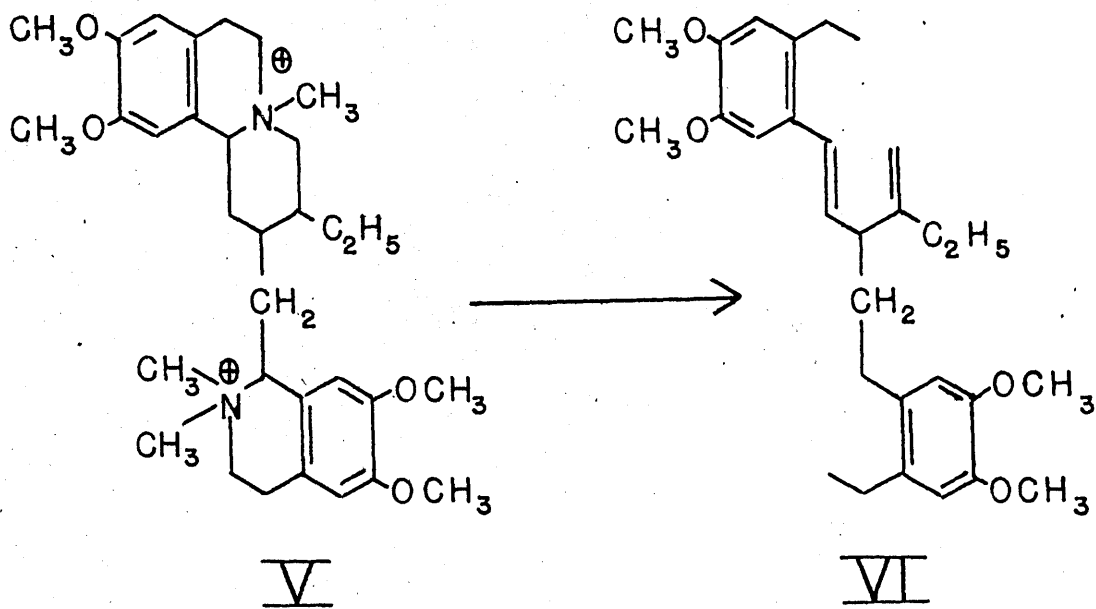
products. The major part of their work consisted of two systematic degradations, accomplished by several repetitions of the reaction sequence--N-methylation, Hofmann degradation, hydrogenation of the resulting olefin. These decompositions, omitting intermediate stages, are indicated on pages 10 and 11 (19,20).

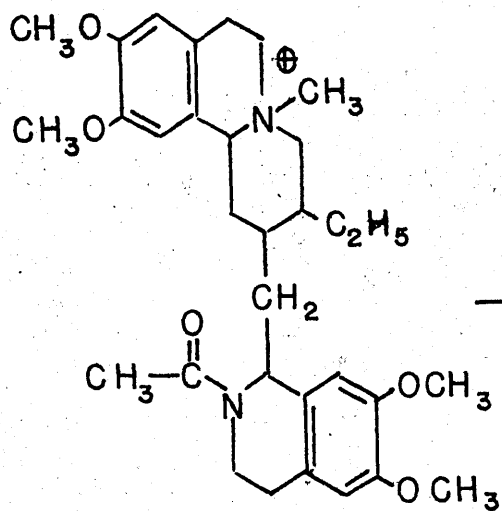
Both degradations yielded the same carbonyl compound, IX, which was also prepared by a total synthesis (21). The final piece of evidence for the structure of emetine was based on the degradation of emetine to 3-ethyl-4-methyl-pyridine (XII) (4). Battersby and Openshaw (22) also confirmed the 6-member nature of the middle ring and the location of the ethyl group, using a completely independent approach.

Once the proof of structure of emetine was accomplished, the elucidation of the structures of the other alkaloids was relatively easy.

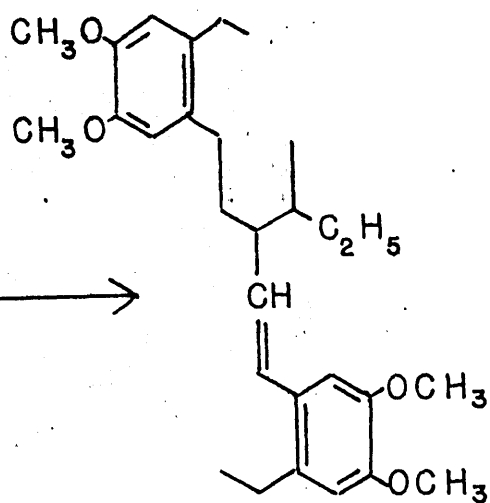
Shortly after their last paper on the emetine proof of structure, Pailer and Porschinski (23) proved the location of the phenolic group in cepheline (XIV). Their method consisted of preparing the O-ethyl ether of cepheline and subjecting it to Hofmann degradations until, by eventual oxidation with ozone, they obtained 2-ethyl-4-ethoxy-5-methoxybenzaldehyde (XIII), indicating that the phenolic group is at position 6' of emetine (IV).

Due to the previously noted relationship, this is also the location of the phenolic group in psychotrine (XV).

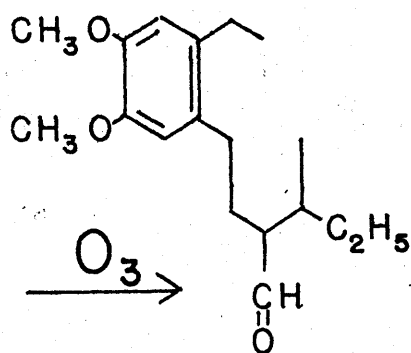




X

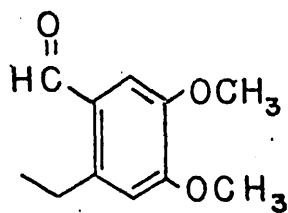


XI

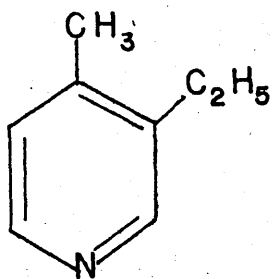


IX

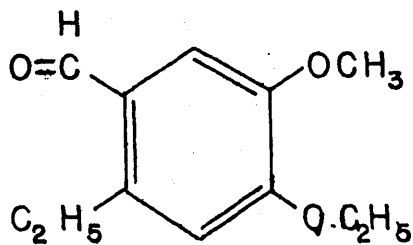
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VII



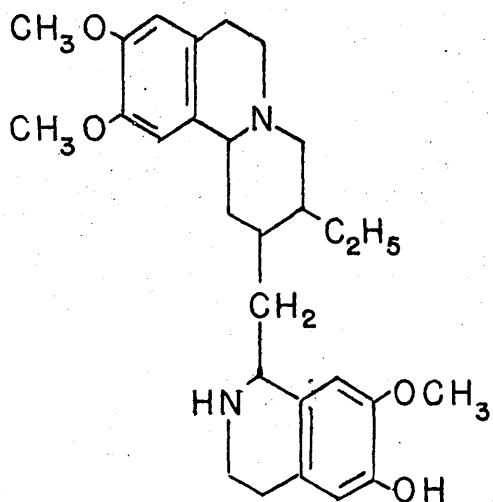
XII



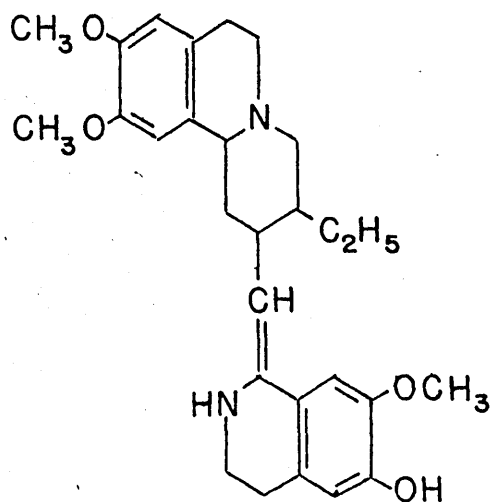
XIII

The double bond in psychotrine and O-methylpsychotrine was established by oxidation and reduction experiments. It had long been known that reduction of O-methylpsychotrine (XVI) yielded both emetine and isoemetine, indicating that an asymmetric atom, of which there are four in emetine, was involved. The really conclusive evidence was supplied by Karrer, Eugster, and Ruttner (6), who oxidized N-benzoyl-O-methylpsychotrine with perphthalic acid and with ozone. From the products they isolated a compound whose elementary analysis was fairly consistent with that required for N-benzoylcorydaldine (XVIII). A synthesis of N-benzoylcorydaldine is reported later in this thesis (24). Its melting point checks with that of the product reported by Karrer, so there seems to be little doubt as to the location of the double bond in psychotrine and O-methylpsychotrine.

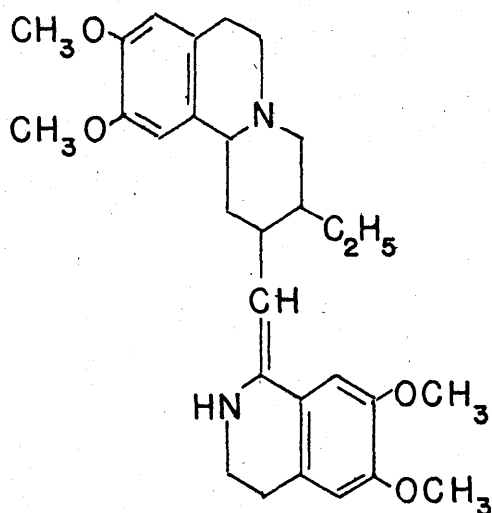
The structure for emetamine (XVII) is based on the following facts: (1.) the tertiary nature of both nitrogen atoms; (2.) the reduction by sodium and alcohol to yield isoemetine; (3.) dehydrogenation of emetine to emetamine.



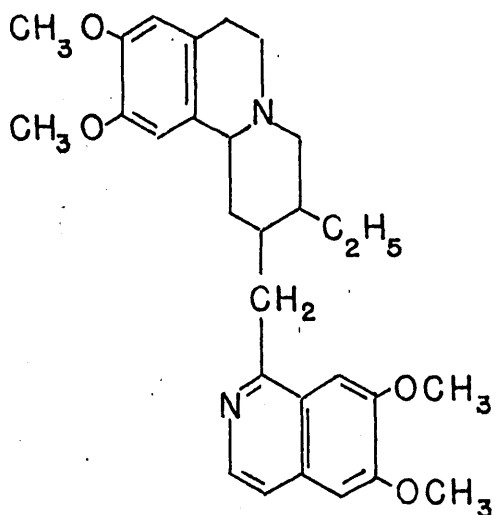
XIV CEPHELINE



XV PSYCHOTRINE

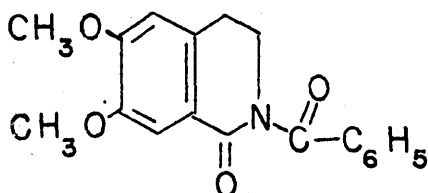


XVI O-METHYLPYCHOTRINE



XVII

EMETAMINE



XVIII

N-BENZOYL CORYDALDINE

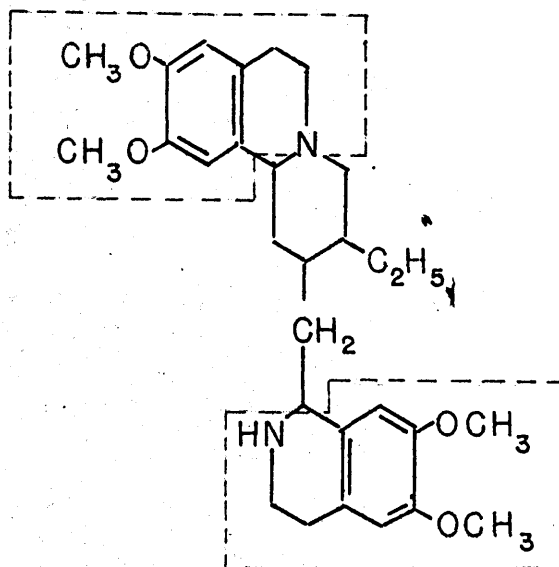
B. Contributions to the Total Synthesis of Emetine

Examination of the emetine molecule (XIX) shows that it may be considered as consisting of two homoveratrylamine (XXI) nuclei, with a branched skeleton containing 9 carbon atoms between them.

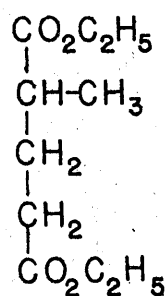
All synthetic attempts reported thus far have employed two molecules of homoveratrylamine, and the problem has reduced itself to the construction of the middle portion, together with the development of methods of attaching the amine nuclei and closing the rings. Three important syntheses have been reported and will be described briefly. The first is the synthesis of a compound corresponding to the formula for emetine postulated by Pyman (I). The second is the synthesis of a racemic compound differing from the accepted formula of emetine only in that it possesses one additional double bond. The third is claimed to be a synthesis of a racemic emetine.

About the time that Pailer and co-workers completed their proof of structure of emetine, Sugasawa (25,26,27) in Japan succeeded in synthesizing a compound having the Pyman structure (I). Since this compound is very closely related to emetine, its synthesis is of considerable interest.

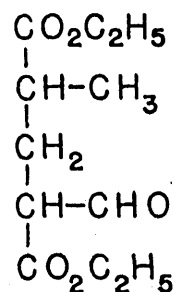
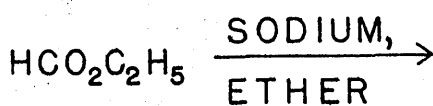
The intermediate, XX, obtained from ethyl α -methylglutarate and ethyl formate, was combined with homoveratrylamine (XXI), and the resulting Schiff base (XXII) was reduced



XIX



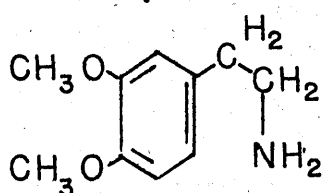
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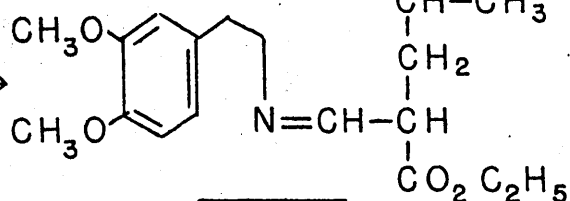
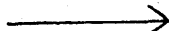
XX

XX

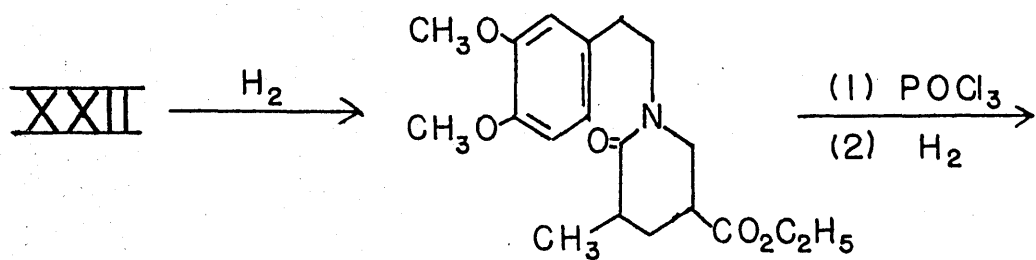
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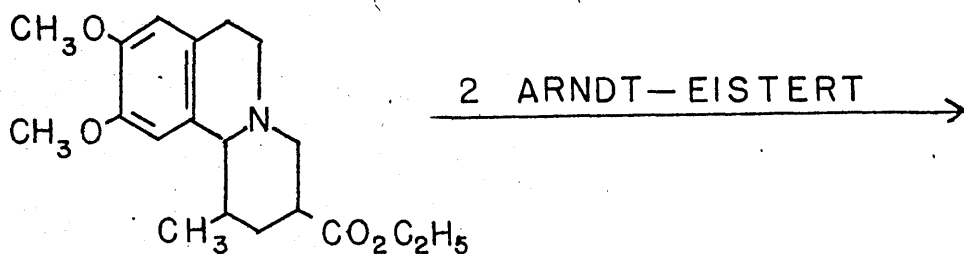
XXI



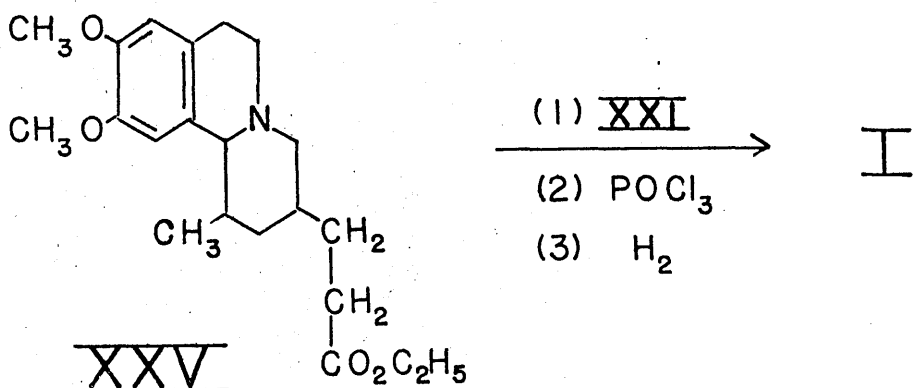
XXII



XXIII



XXIV



XXV

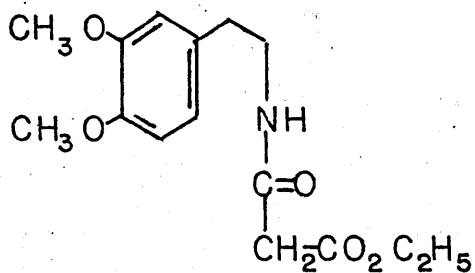
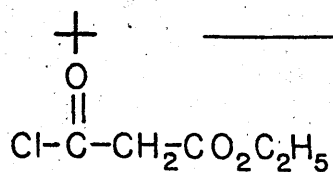
in the presence of platinum oxide. The resulting product, (XXIII), was then subjected to a standard Bischler-Napieralski ring closure, employing phosphorous oxychloride in benzene, and the isoquinoline derivative separated as the quaternary ammonium iodide. The latter salt was converted to the chloride and catalytically reduced to 4',5'-dimethoxy-6-carbethoxy-8-methyl-3,4,5,6,7,8-hexahydrobenzo-[1',2',1,2]-quinolizine (XXIV).

Thus, three of the five rings were complete, with the carbethoxy group available for attaching the rest of the molecule. The latter was accomplished by means of two Arndt-Eistert reactions, condensation of the resulting ester (XXV) with homoveratrylamine, followed by a Bischler-Napieralski ring-closure and reduction.

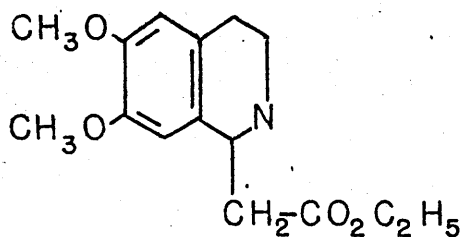
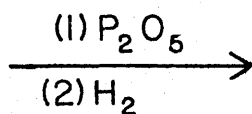
Over a year ago Battersby and Openshaw (28) reported the synthesis of a compound, XXXII, apparently differing from emetine in having a double bond in the 1'-2' position. Their general method of synthesis resembles that of Sugasawa in that they also began with the upper part of the molecule.

The amide (XXVI) obtained from homoveratrylamine and carbethoxyacetyl chloride was subjected to a Bischler-Napieralski ring closure with phosphorous pentoxide and then reduced to the tetrahydroisoquinoline (XXVII). Treatment of the latter with ethyl α -formylbutyrate, followed by reduction, gave the diethyl ester (XXVIII). The third ring of emetine was formed by a Dieckmann condensation of XXVIII, followed

XXI

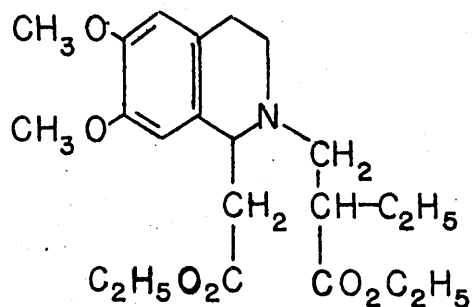
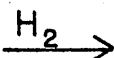
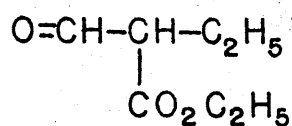


XXVI

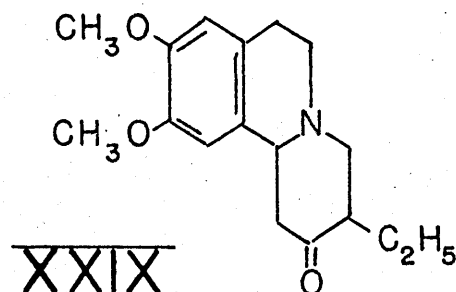
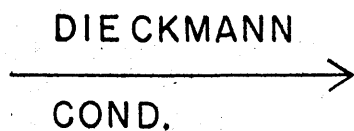


XXVII

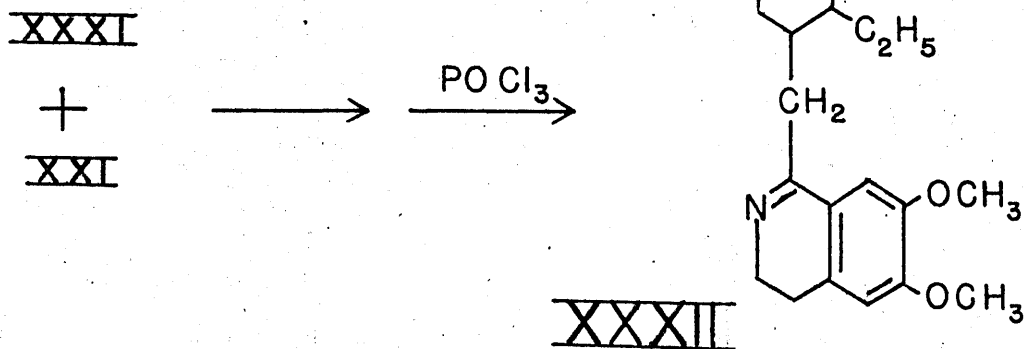
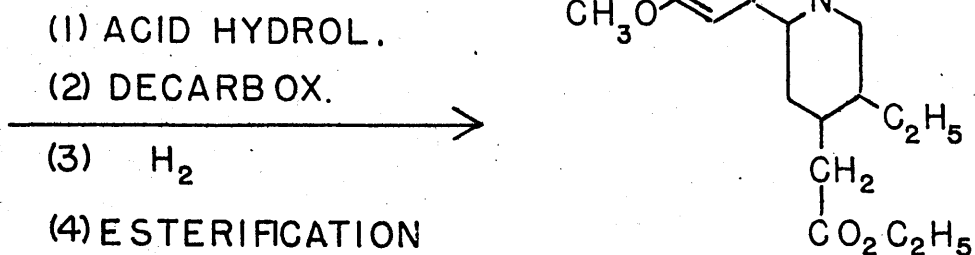
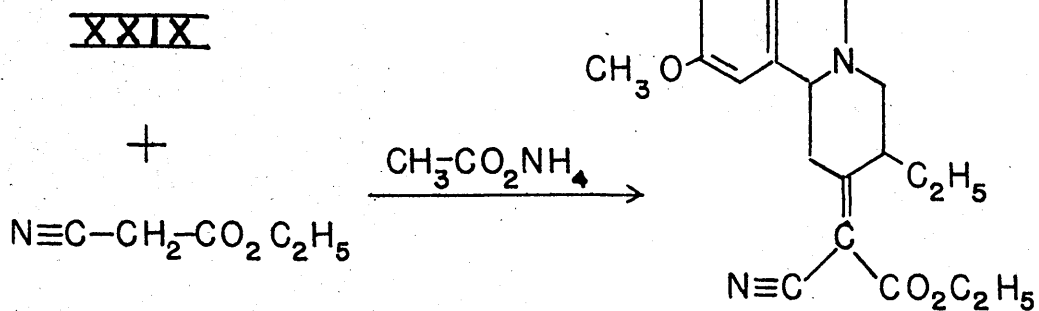
XXVII



XXVIII



XXIX



by hydrolysis to the ketone (XXIX).

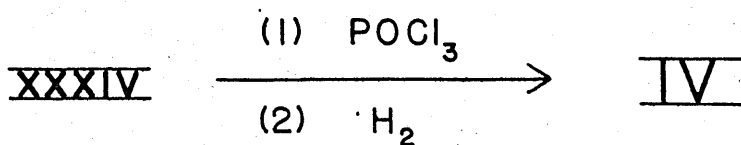
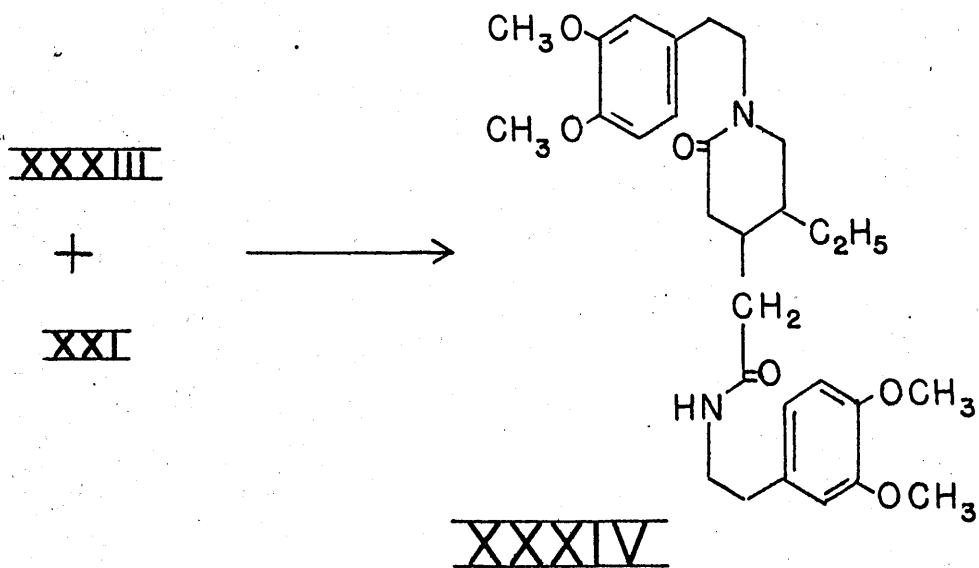
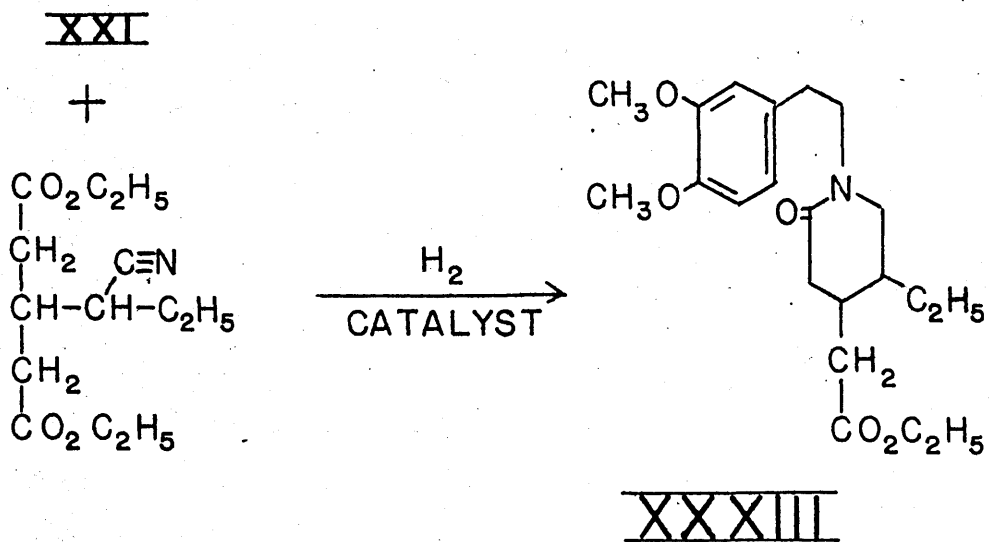
In order to attach the lower portion of the molecule, ethyl cyanoacetate was condensed with XXIX at the keto position, and the condensation product (XXX) subjected to acid hydrolysis, decarboxylation, hydrogenation, and esterification. The resulting ester (XXXI) was then condensed with homoveratrylamine and ring-closed with phosphorous oxychloride, yielding the dihydroisoquinoline (XXXII).

This compound was oxidized with mercuric acetate to dl-rubremetinium bromide, apparently the racemic form of that obtained from emetine. Yet, although XXXII differs from emetine only by the one additional double bond, there has been no report of its reduction to emetine (or isomers of emetine) as yet.

Recently, Evstigneeva and co-workers (5) in Russia have reported the synthesis of a racemic emetine. Unfortunately, this paper contains no experimental description of their work, and until such a description appears or someone else confirms their work, this synthesis cannot be unequivocally accepted.

Their method resembles Sugasawa's in that the middle ring is closed first, but whereas each homoveratrylamine molecule is introduced separately, the two isoquinoline rings are closed at the same time.

In the first stage of this synthesis, ethyl β -(1-cyanopropyl)-glutarate and homoveratrylamine were subjected



to hydrogenation in the presence of nickel or platinum oxide, causing condensation between the amine and cyano group, reduction of the resulting imine group with splitting off of ammonia, followed by condensation of a carbethoxy group with the amino nitrogen. The resulting cyclic amide (XXXIII) was condensed with another molecule of homoveratrylamine at the remaining carbethoxy group, yielding the diamide (XXXIV). The latter was then ring-closed with phosphorous oxychloride and reduced to a racemic emetine.

The same product was also obtained by a variation of the above sequence, in which the amide (XXXIII) was subjected to ring-closure of the upper isoquinoline group before reaction with the second molecule of homoveratrylamine.

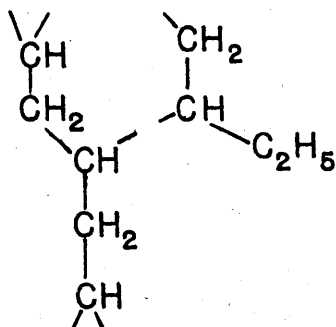
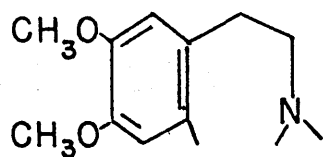
ATTEMPTED SYNTHESSES AND RESULTS

A. Introduction

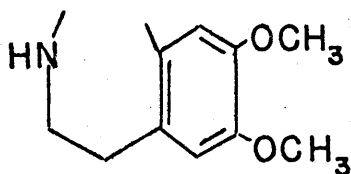
The attempted syntheses of emetine described here differ from those on the preceding pages in that the procedure was designed to introduce the two homoveratrylamine molecules simultaneously by reacting them with a β -substituted glutaric acid or its ester, which could eventually be converted into the correct middle portion of the molecule. Examination of the formula of emetine (XXXV) readily shows the apparent simplicity of this general scheme. In each case ethyl acetonedicarboxylate was employed as the starting material for the β -substituted glutaric acid or ester.

There are several references in the literature to the reaction of homoveratrylamine and β -phenethylamine with dibasic acids or their esters. The resulting diamides were also usually subjected to ring closure by the Bischler-Napieralski reaction to prepare di-(3,4-dihydroisoquinoline) derivatives.

Shortly after Brindley and Pyman proposed their structure for emetine (I), Child and Pyman (29), in 1929, reported the preparation of a series of compounds somewhat resembling emetine in nature. Their intent was to see if any of these possessed the amoebicidal properties of emetine. The general plan of their investigation was to prepare

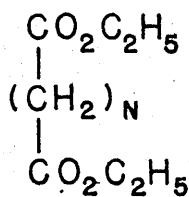


XXXV

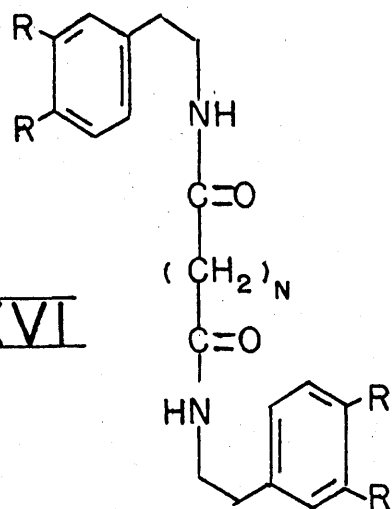


XXI

+

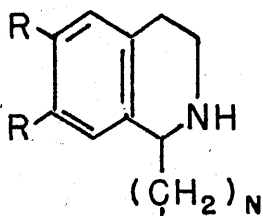


XXXVI



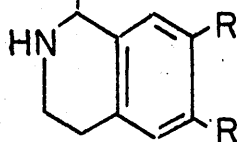
R = H, CH₃O

N = 0, 1, 2, ---- 10



(1) POCl₃, ETC.
(2) [H]

XXXVII



molecules containing two tetrahydroisoquinoline groups connected through the 1 and 1' positions by polymethylene chains (XXXVII). A series of 10 β -phenethylamides and a series of 10 homoveratrylamides were to be subjected to ring-closure and reduction according to the scheme on page 24.

Condensation to the diamides (XXXVI) was readily achieved in all 20 cases, with yields of 50-80%, by heating the reactants (2:1 ratio) for 4 hours at 180°. The only by-products isolated were N- β -phenethylsuccinimide and N-homoveratrylsuccinimide (n=2).

Ring-closure attempts were not as universally successful. In the β -phenethyl series (R=H), one ring of the oxalic derivative (n=0) could be closed, but from malonic (n=1) through sebacic (n=8) no ring-closed products were obtained. As ring-closure agents phosphorous oxychloride, phosphorous pentoxide and a mixture of phosphorous pentachloride and aluminum chloride were employed. In the homoveratryl series (R=OCH₃), however, ring-closure was successful, with phosphorous oxychloride as the agent, on the diamides of adipic and succeeding acids (n=4,5,6,7,8,9,10).

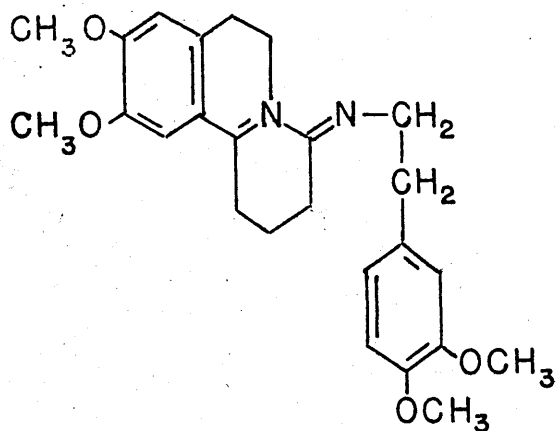
Only three of the 6,7-dimethoxy-3,4-dihydroisoquinoline compounds were reduced to the tetrahydro derivatives (XXXVII) (n=4,5,8), these reductions readily being accomplished by means of tin and hydrochloric acid. None of the dihydro or tetrahydro compounds proved to be effective in preventing the growth of Entamoeba histolytica in cultures.

Although N,N'-dihomoveratrylglutaramide failed to undergo the desired ring-closure, two crystalline materials were isolated as salts from the reaction mixture. On the basis of elemental analysis, one was assumed to be the product obtained by closure of one ring, and the structure, XXXVIII, was postulated for the other.

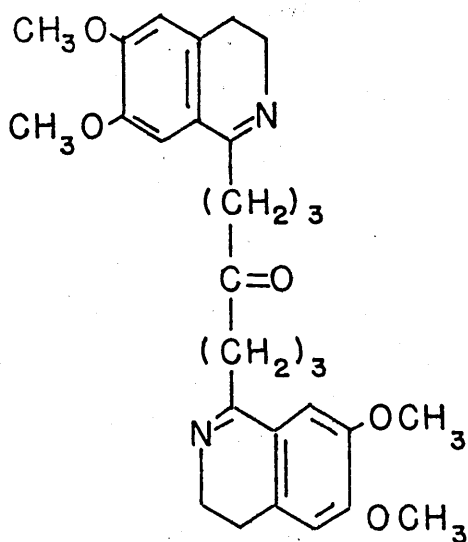
In a similar series of experiments, Hahn and Gudjons (30) reacted homoveratrylamine with dibasic acids themselves, rather than with their esters as Child and Pyman had done. They employed the same simple method, namely heating for 2 to 4 hours in an oil-bath at 180-200°, and reported yields of at least 95% in each case (n=2,3,4,---8). However, they did not report any imide formation with succinic acid.

Ring-closure experiments verified Child and Pyman's experiments. They were unable to isolate crystallizable products after treating the homoveratrylamides of succinic and glutaric acids with phosphorous oxychloride, but the others ring-closed readily, giving yields of 90% or more in most cases. The dihydroisoquinoline compounds were readily reduced to the tetrahydro derivatives by a variety of methods.

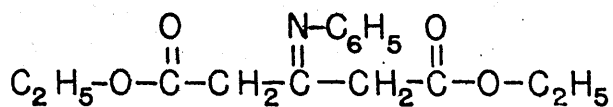
Another synthesis of this type, carried out by King and Robinson (31), is of somewhat greater interest in regard to the present work because of the presence of a keto group in the dibasic acid. These workers reacted homoveratrylamine with dimethyl δ -ketoazelate, and, as in the previous cases, followed this by ring-closure with phosphorous oxychloride.



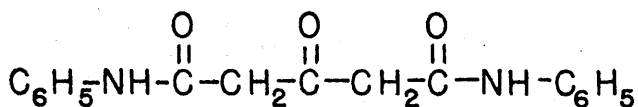
XXXVIII



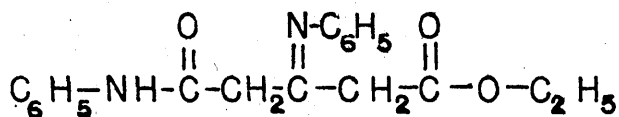
XXXIX



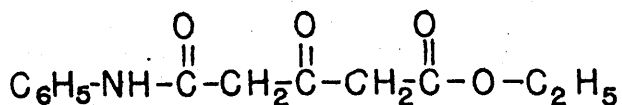
XI



XLI



XLII



XLIII

The diamide formation was accomplished in good yield in exactly the same way as previously described; namely, by heating the amine and ester in a 2:1 ratio for two and one-half hours in an oil-bath at $170-80^{\circ}$. Ring-closure was accomplished by the use of phosphorous oxychloride in toluene, and the product was purified as the picrate. These authors did not report the reduction of this dihydro compound (XXXIX).

The melting points of most of the above diamides and their ring-closed derivatives are in the range of $130-80^{\circ}$; each series shows the alternating magnitude of melting points characteristic of dibasic acids. For a given value of n , the β -phenethylamide, the homoveratrylamide, and the latter's ring-closed product usually melt within less than 10° of each other.

References to reactions between amines and ethyl acetone-dicarboxylate are scanty, and those found pertain to aromatic amines. Besthorn and Garben (32) obtained four products by reacting aniline with ethyl acetone-dicarboxylate. When aniline and this ester in 1:1 ratio stood for three days at room temperature, the only product was the Schiff base, ethyl β -(phenylimino)-glutarate (XL). A second reaction was carried out at 100° for 24 hours with an amine:ester ratio of 1.3:1. Three products were obtained: N,N'-diphenyl- β -ketoglutaramide (XLI), 21%; N-phenyl- β -(phenylimino)- γ -carbethoxybutyramide (XLII), 29%; N-phenyl- β -keto- γ -carbethoxybutyramide (XLIII), 0.3% (yields based upon aniline).

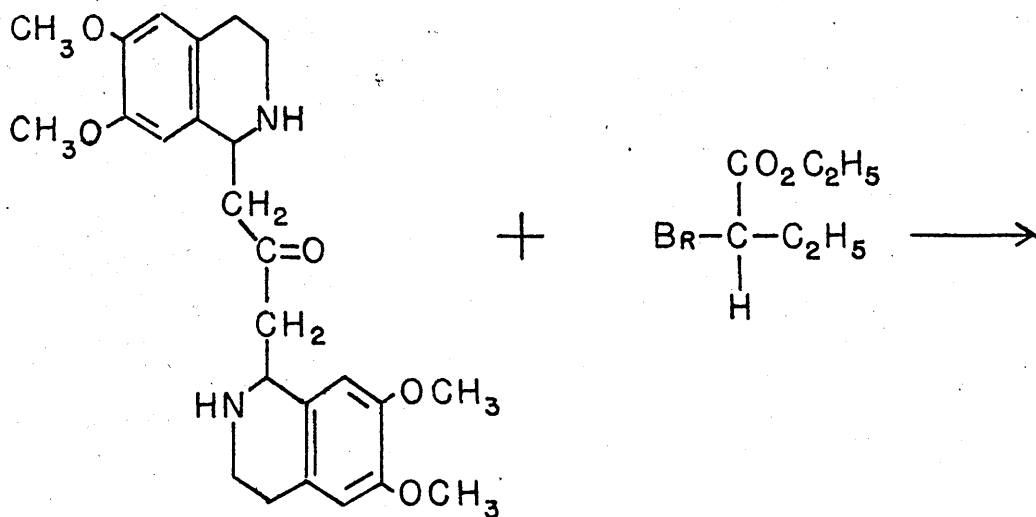
Naik and Thosar (33) have reported the preparation of the di-(α and β)-naphthylamides of acetonedicarboxylic acid. These compounds correspond to the formula XLI, with α - or β -naphthyl groups in place of the phenyl groups.

B. Experiments Leading to the Synthesis of N-Benzoylcorydaldine.

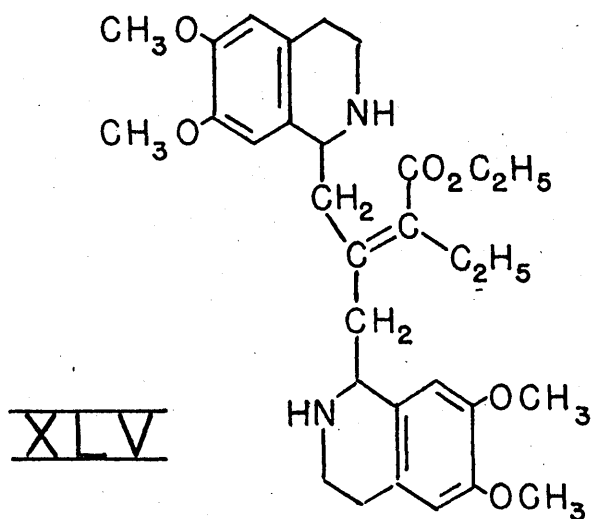
The first synthesis attempted was based upon the direct condensation of ethyl acetonedicarboxylate with homoveratrylamine. Briefly, the plan was to react two molecules of homoveratrylamine with the ester, and follow this by Bischler-Napieralski ring-closure and reduction. The resulting s-bis-(6,7-dimethoxy-1,2,3,4-tetrahydro-1-isoquinolyl)-acetone (XLIV) was to be combined with ethyl α -bromobutyrate in a Reformatsky reaction to produce the intermediate, XLV. The synthesis would be completed by reduction, ring-closure and another reduction. It was assumed that the secondary amino groups would have to be inactivated by acylation at various stages. Also, various other plans could be devised to convert XLIV to the emetine skeleton.

Due to the limited quantity of homoveratrylamine available, β -phenethylamine was employed in several preliminary experiments. By employing a variety of reaction conditions two products were obtained from each amine, but these four materials represent only 3 different types of compounds.

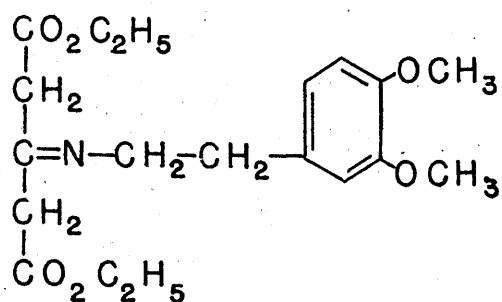
In the first experiment, homoveratrylamine was reacted with ethyl acetonedicarboxylate according to the general method of Child and Pyman (pp. 23-28), that is, by simply heating the reactants in an oil-bath at 170-80°. A small yield of white solid, m.p., 79-80°, was obtained, which, according to elemental



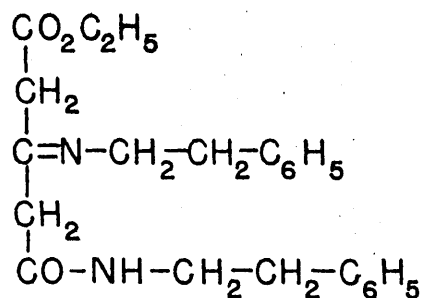
XLIV



XLV



XLVI



XLVII

analysis, is apparently the Schiff base, ethyl β -homoveratryliminoglutamate (XLVI), produced by a 1:1 reaction between the amine and keto group.

When homoveratrylamine and ethyl acetonedicarboxylate are mixed, solidification occurs quite rapidly, accompanied by a moderate evolution of heat. The same product (XLVI) was obtained in practically 100% yield by allowing the ester and amine to react at room temperature.

After these first experiments with homoveratrylamine, β -phenethylamine was substituted. By employing a variety of reaction conditions, ranging from room temperature to 180°, a product, m.p., 112-114°, was obtained whose analysis indicated that it was not analogous to the previous homoveratrylamine derivative (XLVI). Its percentage carbon and hydrogen agree very closely with that required for N-(β -phenethyl)-3-(β -phenethylimino)-4-carbethoxybutyramide (XLVII), but several analyses all gave nitrogen values ranging from 0.5 to 1.0% too high. However, this was the only reasonable structure that could be devised for this substance.

In the next series of reactions homoveratrylamine and ethyl acetonedicarboxylate were mixed in a 3:1 ratio and reacted at a higher temperature. The reaction flask was attached to a short column and heated until a reasonable yield of liquid boiling at 78° had been collected. This was assumed to be ethanol plus, perhaps, some water. From the residue, a good yield of white leaflets, m.p., 151-152°, was obtained,

which, by coincidence, gave a carbon, hydrogen, and nitrogen analysis fairly close to that required by N,N'-dihomoveratryl- β -(homoveratrylimino)-glutaramide (XLVIII).

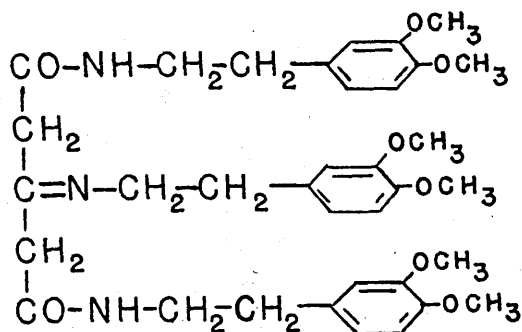
Calcd. for $C_{35}H_{45}O_8N_3$: C, 66.12; H, 7.14; N, 6.61

Found: 64.95 7.03 7.23

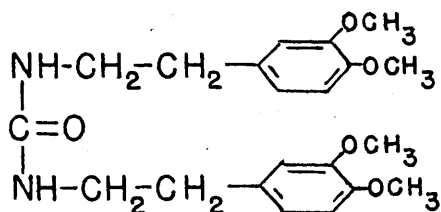
As a result of this coincidence, several unsuccessful attempts were made to hydrolyze the Schiff base group believed present, but the unknown product proved to be most stable, contrary to all literature reports on Schiff bases. Further analyses, based upon highly purified samples, failed to give closer nitrogen values, so it was quite apparent that the reaction had taken a completely different course.

Investigation of the literature revealed the identity of the product to be s-bis-homoveratrylurea (XLIX). Similar reactions have also been reported. The only previous preparation of s-bis-homoveratrylurea was recorded by Mohunta and Ray (34), who, oddly enough, also obtained it as an unexpected reaction product. They attempted to react β -(3,4-dimethoxyphenyl)-ethylisocyanate with acetic anhydride in xylene to obtain N-homoveratryl-N-acetylacetamide, but obtained instead s-bis-homoveratrylurea. They attributed this turn of events to the presence of water in the xylene.

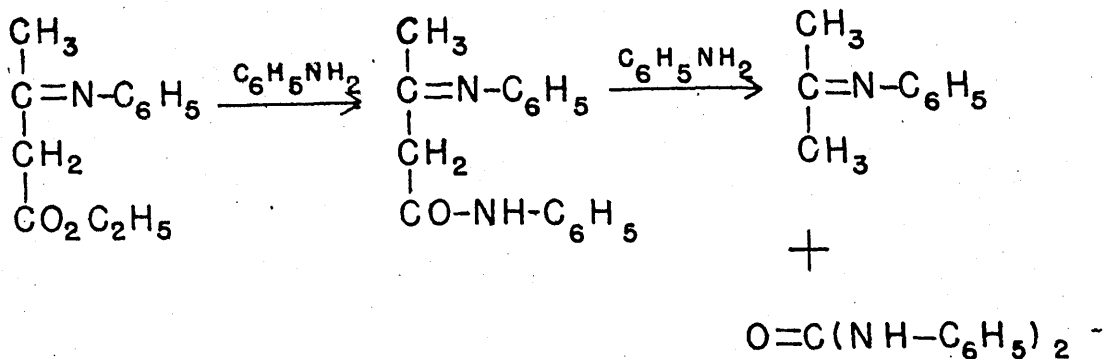
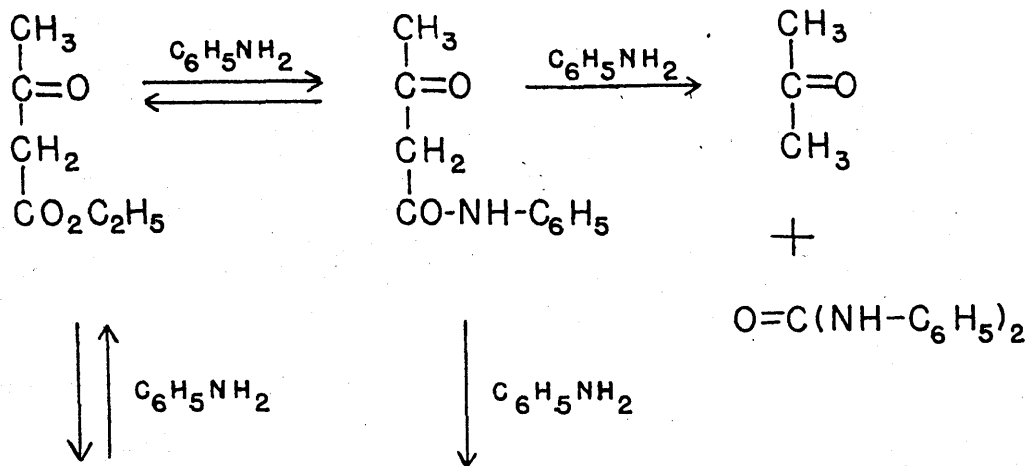
A high temperature reaction between β -phenethylamine and ethyl acetonedicarboxylate yielded the analogous s-bis-(β -phenethyl)-urea, m.p., 138-138.5°. Curtius and Jordan (35) prepared this compound, m.p., 137°, from β -phenyl-



XLVIII



XLIX



I

ethylisocyanate and water, and it has also been prepared from other derivatives of dihydrocinnamide (36,37).

A recent paper by Roberts and Edwards (38) discusses the mechanism of the reaction between ethyl acetoacetate and aniline to form s-diphenylurea. They list 7 isolated, scattered references to the reaction of β -keto esters with aniline to yield s-diphenylurea. Most of these were also with acetoacetic ester. According to Roberts and Edwards the reaction proceeds according to the scheme (L).

In carrying out this reaction they heated the amine and ester (2:1 ratio) at 190° liquid temperature, maintaining aniline reflux half-way up a short Vigreux column. The distillate was condensed and analyzed for acetone. In arriving at the mechanism, the proposed intermediates were also used as starting materials.

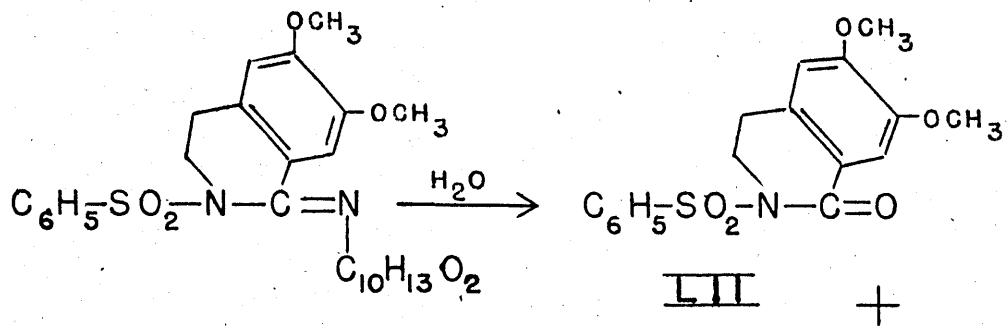
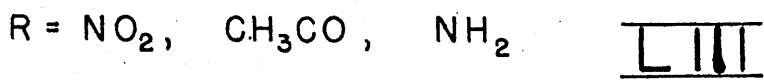
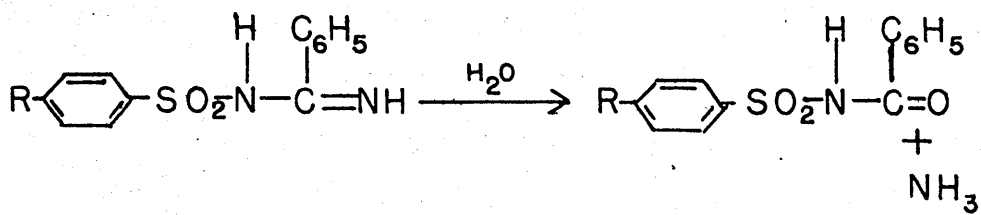
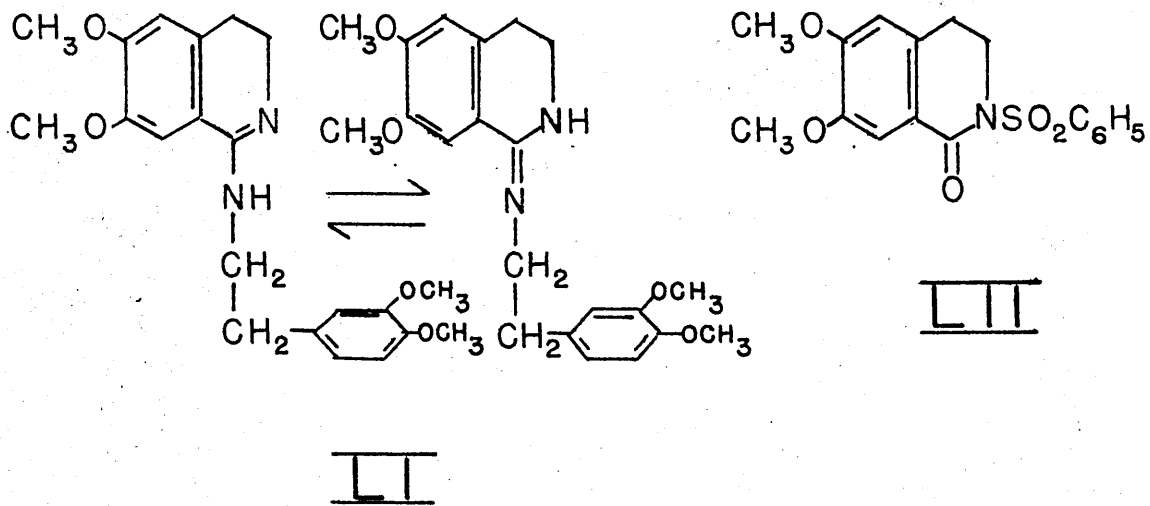
Before the true identity of s-bis-homoveratrylurea was recognized, a Bischler-Napieralski ring-closure was attempted. This proved to be a fortunate move since it eventually lead to the synthesis of N-benzoylcorydaldine. The reaction was carried out in xylene with phosphorous pentoxide as the dehydrating agent, and this caused one ring to close, thereby forming a cyclic amidine, 1-homoveratrylamino-6,7-dimethoxy-3,4-dihydroisoquinoline (LI). The latter was first isolated and analyzed as the phosphate salt, but later the amidine (LI) itself was separated in pure form as a white solid, m.p., 135°.

s-Bis-(β -phenethyl)-urea behaved in a similar manner with phosphorous pentoxide in xylene, but this phosphate was not further investigated. When phosphorous oxychloride was employed as a ring-closure agent for s-bis-(β -phenethyl)-urea, most of the latter was recovered, indicating that fairly vigorous ring-closure conditions are required.

Mohunta and Ray (34) carried out similar ring-closures on appropriate urea derivatives, obtaining 1-arylamino-6,7-dimethoxy-3,4-dihydroisoquinolines.

The final step in the synthesis of N-benzoyl corydaldine was accomplished by simply shaking the amidine or its phosphate with benzoyl chloride in the presence of excess 10% sodium hydroxide solution, just as in the Schotten-Bauman reaction. This synthesis was preceded by the analogous preparation of N-benzenesulfonylcorydaldine (LII) by the same procedure, substituting benzenesulfonyl chloride for benzoyl chloride. These corydaldine derivatives possessed nearly identical melting points--194-195° for the benzoyl derivative and 193.4-194.8° for the benzenesulfonyl derivative. Karrer, Eugster, and Ruttner report a melting point of 195-196° for their product from oxidation of N-benzoyl-O-methylpsychotrine.

Mohunta and Ray (34), who were trying to develop a synthesis of corydaldine, attempted to hydrolyze their 1-aryl-amino-6,7-dimethoxy-3,4-dihydroisoquinoline derivatives to corydaldine, but recovered their starting materials. Their report mentions only an attempted hydrolysis in hydrochloric



LTV

XXI

acid and gives no experimental details for this portion of their work. Attempts to hydrolyze 1-homoveratrylamino-6,7-dimethoxy-3,4-dihydroisoquinoline (LI) in this laboratory were unsuccessful also. After several hours boiling in dilute sodium hydroxide the amidine was recovered almost completely. Although a separate acid hydrolysis experiment was not performed, the ring-closure reaction mixture was decomposed with water and steam-distilled for one hour to remove xylene, which was equivalent to boiling the amidine in dilute phosphoric acid. A good yield of the amidine phosphate was the only product isolated. While most amidines are fairly readily hydrolyzed, others of marked stability have been reported in the literature (39).

In contrast to the stability of the amidine in boiling sodium hydroxide solution alone, the addition of benzoyl chloride or benzenesulfonyl chloride permits the ready removal of the 1-amino group by merely shaking in cold alkaline solution. This is assumed to be due to prior reaction of the benzoyl or benzenesulfonyl group at the ring nitrogen. A somewhat similar hydrolysis is reported by Barber (40) who prepared a series of sulfonyl derivatives of amidines and imino ethers. The analogy between Barber's hydrolyses and those described above is indicated by the equations on page 37. Actually no attempt was made to isolate the postulated intermediate (LIV).

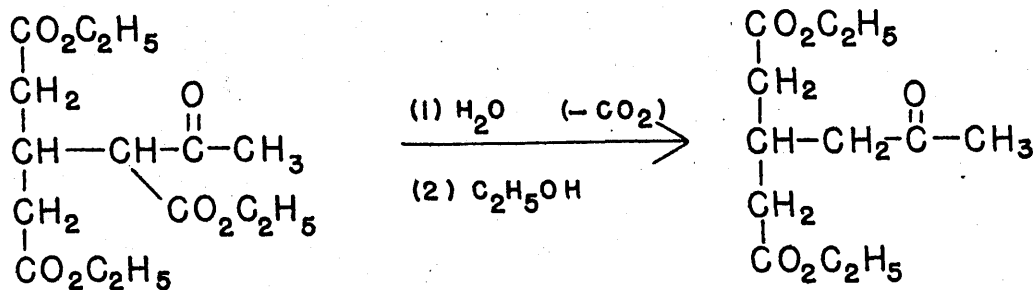
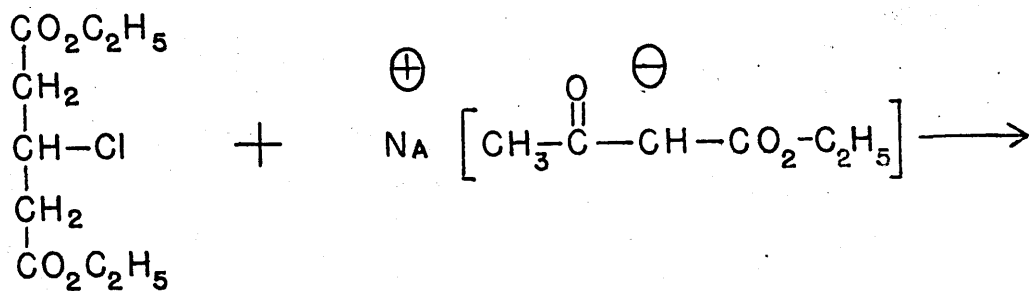
C. Synthetic Efforts Based upon Ethyl β -Acetonylglutarate

Since the desired first step of the previous plan for the total synthesis of emetine could not be accomplished, the next attempted synthesis was based upon first preparing a α -substituted glutaric ester, and then reacting this with homoveratrylamine.

Ethyl acetonedicarboxylate was again employed as a starting material, but it was converted to ethyl β -acetonylglutarate (LVI) before attempting combination with homoveratrylamine to form the diamide (LVII). It was hoped that the latter could be ring-closed and reduced to the tetrahydroisoquinoline compound (LVIII). The middle ring of the alkaloid would then be closed by a Mannich reaction (LIX), and the synthesis completed by reduction of the acetyl group.

Ethyl acetonedicarboxylate was quantitatively reduced to ethyl β -hydroxyglutarate by reduction at 2-3 atmospheres of hydrogen in a Parr apparatus, using platinum oxide as a catalyst. The hydroxy ester was converted to ethyl ω -acetyl-methanetriacetate (LV) according to the method described by Dreifuss and Ingold (41). Although the intermediate, ethyl β -chloroglutarate, and the condensation product (LV) were not purified, the yields were probably at least 80% for each step. Dreifuss and Ingold report 87% and 80% yields, respectively.

A combined hydrolysis and decarboxylation was carried



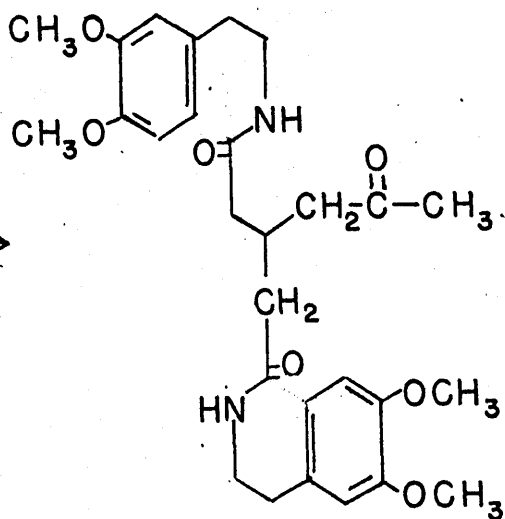
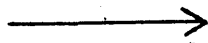
LV

LVI

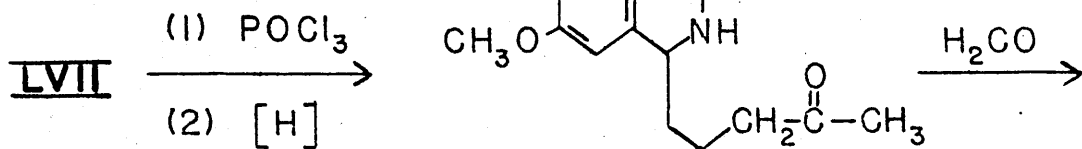
LVI

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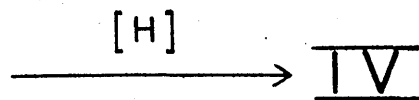
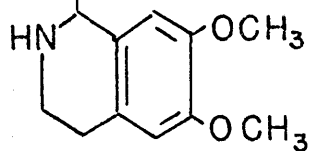
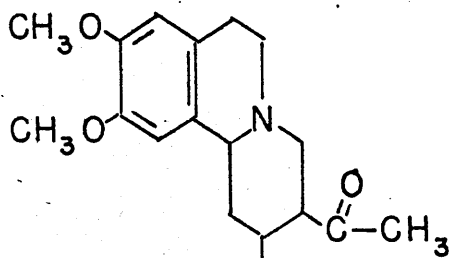
XXI



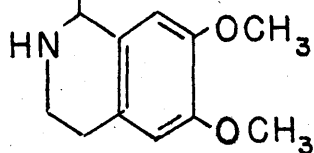
LVII



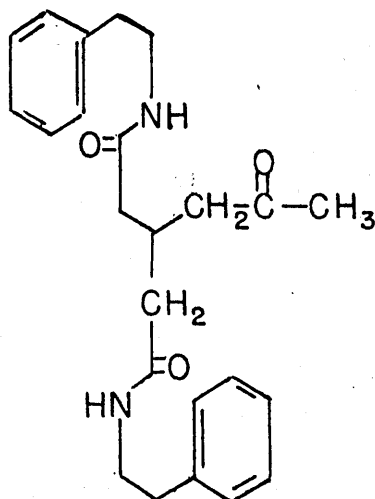
LVIII



LIX



LX



out with 4 N hydrochloric acid by the method of Bentley and Perkin (42), who decarboxylated the closely related α -acetylglutaric acid to γ -acetylbutyric acid. The course of decarboxylation was followed by collecting the evolved carbon dioxide in a graduate cylinder by displacement of water. After 5 hours, evolution practically ceased and approximately 100% of the theoretical amount of carbon dioxide had been evolved; only a 60% yield of the dibasic acid was obtained. Since the intermediates had not been purified, this is not surprising, and the extra carbon dioxide was probably obtained from excess ethyl acetoacetate.

β -Acetonylglutaric acid is not reported in the literature and could not be obtained in crystalline form, so it was esterified according to the procedure described in Organic Syntheses (43) for the esterification of adipic acid. Based upon the β -acetonylglutaric acid of unknown purity, the yield of crude ester was 57%. This represents an overall yield of 27% for the 4-stage synthesis of ethyl β -acetonylglutarate. This ester was distilled at 139-140° (3.5 mm.), and its elemental analysis was very close to theoretical. Both β -acetonylglutaric acid and its ester gave positive iodoform tests.

As in the case of ethyl acetonedicarboxylate, the first attempts to prepare the di-homoveratrylamide of β -acetonylglutaric acid were by the simple method of Child and Pyman (p. 23-8). It was thought that ethyl β -acetonylglutarate might behave similarly to King and Robinson's methyl

δ -ketoazelate (31), inasmuch as both contain a δ -keto group. However, only tarry residues were obtained.

When β -phenethylamine was employed in place of homoveratrylamine, a low yield (c.a. 5%) of crystalline product was obtained. From a run using commercial β -phenethylamine, two white solids were recovered, melting at 170.6-171.4°, and 151-153°. Elemental analysis of the lower melting material checked quite well with that calculated for N,N'-di(β -phenethyl)- β -acetylglutaramide (LX), and the higher melting sample was also in this range of percentage composition. Later reactions with freshly-distilled β -phenethylamine yielded only the product of m.p. 151-153°. It was discovered that increasing the amine to ester ratio increased the yield of amide; at 20:1, a yield of 23%, based upon ester, was obtained. This represents barely 6% overall yield based upon the original starting material, ethyl acetonedicarboxylate.

The high amine to ester ratio was also employed with homoveratrylamine, but the only solid product isolated was a yield of about 5% of a tan, powdery solid, which melted to a red liquid at 60-80°. On the basis of comparison with similar compounds, the desired diamide (LVII) should melt in the neighborhood of 150°.

Ring-closure of LX was attempted with phosphorous oxychloride in toluene. From the tarry reaction product a little tan gummy material was recovered by extraction with hydrochloric acid. This material could not be crystallized,

but a sharp-melting picrate was derived from it in low yield. Elemental analysis of this picrate indicates that it cannot possibly be either the mono- or di-picrate of the desired 1,3-di-(3',4'-dihydro-1'-isoquinolyl)-2-acetonylpropane. There was trace evidence of another picrate melting in the neighborhood of 150°, but because of low yields involved, this method of synthesis was discontinued.

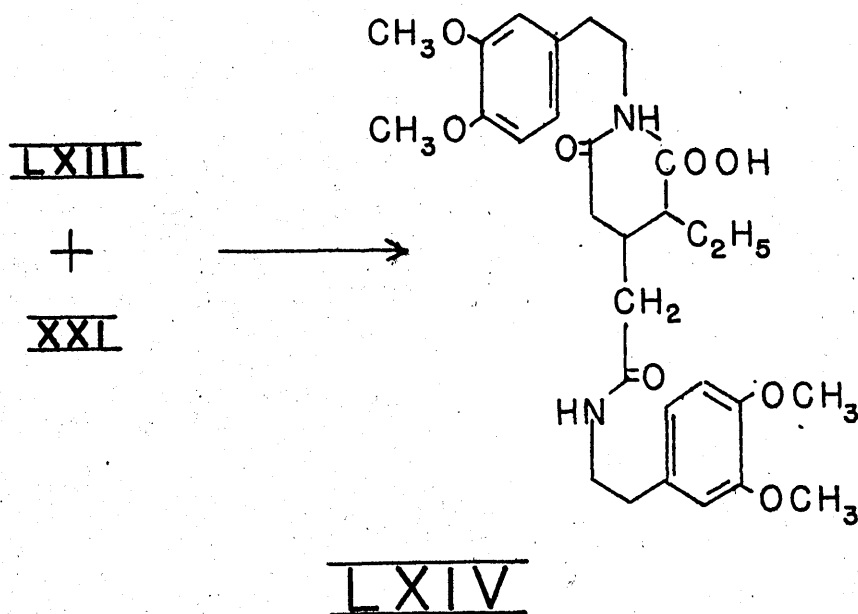
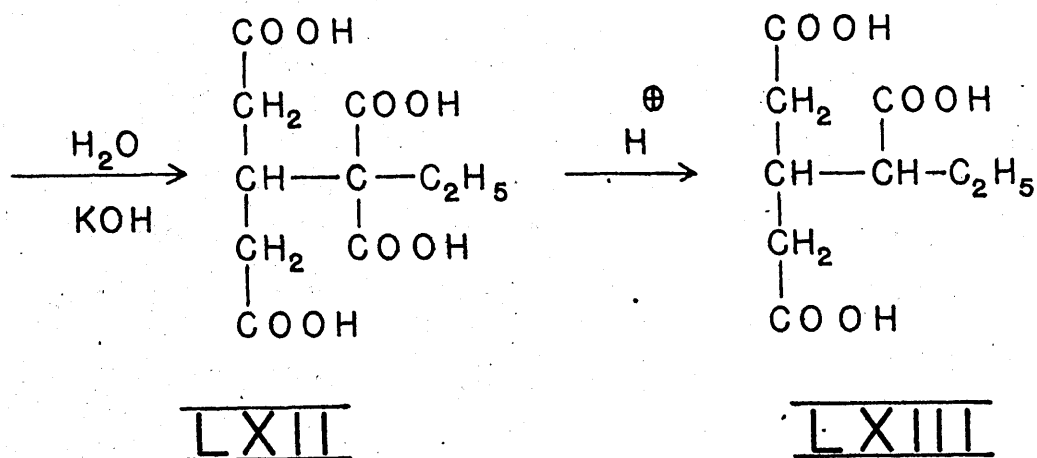
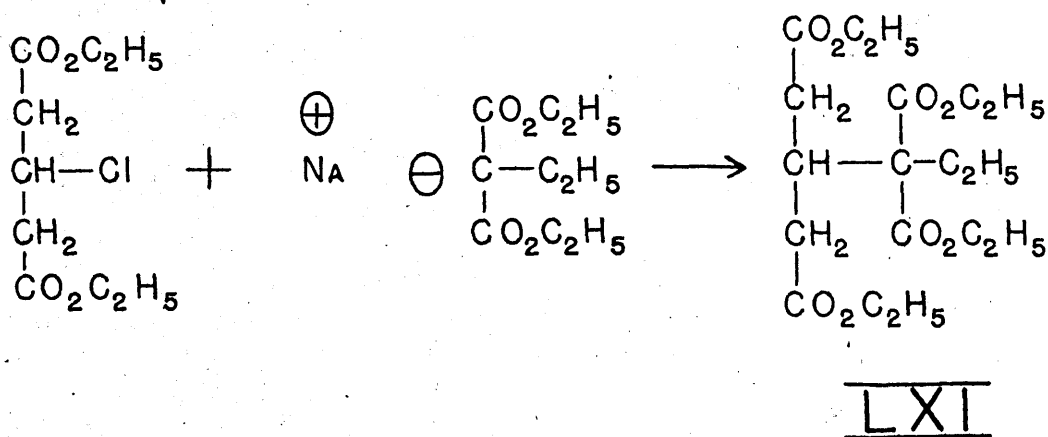
In the hydrolysis and decarboxylation of ethyl ω -acetylmethanetriacetate to β -acetonylglutaric acid, a small yield of a by-product was obtained. This was an acid, m.p. 194-198°, with a neutralization equivalent of 68 \pm 1. It gave a positive iodoform test, and the elemental analysis checks quite closely with that required by ω -acetylmethanetriacetic acid. The neutralization equivalent of the latter is 77, however, and it would seem unlikely that ω -acetylmethanetriacetic acid would decarboxylate fairly rapidly until 90% or so had decomposed and then cease entirely. Thus this substance remains unidentified.

D. Preparation and Decarboxylation of β -(1,1-Dicarboxypropyl)-glutaric acid (LXII).

The third general method of synthesis proposed was to be based upon the reaction of homoveratrylamine with β -(1-carboxypropyl)-glutaric acid (LXIII). It was hoped that, by using exactly two moles of amine per mole of acid (or its ester), the amine would react preferentially with the two carboxyl groups attached to methylene groups and form LXIV as the major product. This seemed a reasonable expectation in that these two carboxyl groups are less sterically hindered than the carboxyl group joined to the secondary carbon atom.

Ethyl β -hydroxyglutarate was condensed with the sodium salt of diethyl ethylmalonate to form ethyl β -(1,1-dicarboxypropyl)-glutarate (LXI), and the latter was hydrolyzed to the corresponding tetracarboxylic acid (LXII). The yield of this acid, m.p., 204-206°, was low (16%); other products isolated included a fairly large yield of ethylmalonic acid (38%), and an appreciable amount on an intractable acidic syrup.

Several decarboxylation experiments failed to yield any of the desired β -(1-carboxypropyl)-glutaric acid (LXIII). When subjected to acid-catalyzed decarboxylation, only a fraction of the theoretical amount of carbon dioxide was evolved, and, in addition to recovered acid, a little gummy resin was obtained. The latter possessed a neutralization equivalent of about 92, as compared to 73 for the desired



tricarboxylic acid. A quantitative thermal decarboxylation was carried out in an oven at 180° , with fairly interesting results. During the first few hours of heating, the white powder slowly changed to a reddish-brown porous resin, plastic while hot and brittle when cold. The weight decreased at the rate of about 4% per hour, accompanied by a steady increase in neutralization equivalent. At the end of 6 hours, when 23% of the weight had been lost, the rate decreased to less than 1% per hour, and the neutralization equivalent remained constant at 100 ± 3 .

If β -(1,1-dicarboxypropyl)-glutaric acid were to lose one molecule of carbon dioxide and one molecule of water, the loss in weight would equal 23.6%, and the resulting product would have a molecular weight of 200. However, if the product is the simple anhydride of a tricarboxylic acid, it should have a neutralization equivalent of 67 (assuming hydrolysis of the anhydride). Yet, the product obtained had a neutralization equivalent of 100, indicating that, in addition to the loss of one acid group by decarboxylation, another acid group has been neutralized in some way.

These quantitative comparisons may be mere coincidences, and since a polymer of some type seems to have been formed, the investigation of this reaction was beyond the scope of the present work.

EXPERIMENTAL*

A. Reactions of Ethyl Acetonedicarboxylate with Homoveratrylamine and β -Phenethylamine.

a. Ethyl β -(homoveratrylimino)-glutarate (XLVI).

Five grams (0.028 mole) of homoveratrylamine and 2.80 g. (0.014 mole) of ethyl acetonedicarboxylate were mixed in a large test tube, solidification occurring with evolution of heat. This mixture was heated for two hours at 170-180° in an oil-bath. A dark-red viscous syrup resulted. When the latter was cooled in an ethanol-dry ice bath, a white solid separated, which amounted to 0.6 g. (12%) after washing with cold ethanol, m.p. 77.5-78.5°. Recrystallization from methanol produced pure white leaflets, m.p. 79.2-79.8°.

Anal. Calcd. for $C_{19}H_{27}NO_6$: C, 62.47; H, 7.40; N, 3.85

Found:	62.84	7.38	4.31
	62.87	7.58	4.02

When 21.0 cc. (0.125 mole) of homoveratrylamine and 19.0 cc. (0.10 mole) of ethyl acetonedicarboxylate were mixed, heat was evolved accompanied by formation of a white solid. When the reaction appeared to be complete, the product was

*All melting points are corrected. Analyses by Oakwold Laboratories, Alexandria, Virginia, and by Strauss and Weiler, Microanalytical Laboratory, Oxford, England.

crystallized from absolute ethanol, yielding 37.1 g. (100%) of colorless leaflets melting at 68-73°. Several recrystallizations from absolute ethanol brought the melting point up to 79.2-79.8°.

b. N-(β -phenethyl)-3-(β -phenethylimino)-4-carbethoxybutyramide (XLVII), (probable identity).

Six grams (0.047 mole) of β -phenethylamine and 5.0 g. (0.025 mole) of ethyl acetonedicarboxylate were heated in a closed flask at 100° for 20 hours. The dark-red liquid which resulted was dissolved in 300 cc. of ether, extracted with dilute hydrochloric acid, washed with water, and dried over calcium chloride. After evaporating the ether solution to 50 cc. and cooling in an ice-bath, 1.2 g. (13%) of a white solid crystallized. Recrystallizations from ether and from ligroin gave anomalous melting points, ranging from 112 to 119°, depending on the solvent, length of drying time, and rate of heating during the melting point determination. The highest m.p. obtained was 118.6-119.4°.

Anal. Calcd. for $C_{23}H_{28}O_3N_2$: C, 72.60; H, 7.42; N, 7.36

Found:	72.85	7.39	8.23
	72.84	7.18	7.80

The same product was obtained by allowing 10.0 g. (0.0495 mole) of the ester and 18.0 g. (0.149 mole) of the amine to stand for eleven days at room temperature. A yield of 12.3 g. (65%) of crude product was obtained, which showed

a m.p. of 111.4-112.4° after several recrystallizations from absolute ethanol.

Anal. Found: C, 72.56, 72.96; H, 7.76, 7.54; N, 8.20, 8.56

This substance was also obtained by heating 5.0 g. (0.025 mole) ethyl acetonedicarboxylate and 6.0 g. (0.047 mole) -phenethylamine for 2 1/2 hours at 170-175°. The initial product was a dark greenish liquid which, upon standing overnight, changed to a mush of white crystals in green oil. This material was mixed with 50 cc. of cold ether, filtered, and washed with a little ether. The air-dried product was slightly greenish and weighed 3.5 g. (37%). A small portion of this was recrystallized from ether, m.p. 112-113°.

c. s-Bis-homoveratrylurea (XLIX).

The mixture of ethyl β -(homoveratrylimino)-glutarate (XLVI) and homoveratrylamine which resulted from adding 50.0 g. (0.25 mole) of ethyl acetonedicarboxylate to 134.5 g. (0.75 mole) of homoveratrylamine, was heated on a Todd column until 26 cc. of liquid had distilled, b.p. 78°. The temperature in the distilling pot was not determined.

Upon cooling, the residue solidified to a tough gum, which was crystallized from absolute ethanol, yielding 63.7 g. (62.5%) of yellow crystals. Further crystallizations from ethanol produced white leaflets, m.p. 151-152°. Mohunta and Ray (34) report 152°, from benzene.

Anal. Calcd. for $C_{21}H_{28}O_5N_2$: C, 64.92; H, 7.26; N, 7.21

Found:	64.95	7.03	7.23
	65.24	6.93	7.30
	65.43	7.26	7.70

d. s-Bis-(β -phenethyl)-urea.

A mixture of 10.0 g. (0.0495 mole) of ethyl acetone-dicarboxylate and 18.0 g. (0.149 mole) of β -phenethylamine was refluxed in a flask joined to a Todd column. In the course of an hour, 6.2 cc. of liquid, b.p. 78° , distilled over. The residual brown gum, after being washed with dilute hydrochloric acid and water, was crystallized from 45 cc. of ethanol, producing 3.3 g. (25%) of yellow-brown solid. When recrystallized from absolute ethanol (Norit) it melted at $140-141^\circ$. Curtius and Jordan (35) report a m.p. of $138-138.5^\circ$ from benzene.

Anal. Calcd. for $C_{17}H_{20}ON_2$: C, 76.06; H, 7.53; N, 10.44

Found:	76.41	7.62	10.90
	76.18	7.75	10.55

B. Bischler-Napieralski Reactions of s-Bis-homoveratrylurea and s-Bis-(β -phenethyl)-urea.

a. 1-(Homoveratrylamino)-3,4-dihydro-6,7-dimethoxy-isoquinoline (LI).

Fifteen grams (0.0385 mole) of s-bis-homoveratrylurea and 23 grams of phosphorus pentoxide were refluxed in 250 cc. xylene for 90 minutes, after which 200 cc. xylene was distilled during the next 45 minutes. To the residue was added 250 cc. water and the mixture steam-distilled to remove the remaining xylene. The distillation residue was diluted with water to 300 cc., heated to boiling, and filtered to remove 2 or 3 g. of dark, tarry material. The orange-colored aqueous filtrate produced 11.5 g. (60%) of light tan solid upon standing overnight. This was crystallized (Norit) from 200 cc. water, yielding 6.7 g. of a white precipitate, m.p. 269-270°. Another recrystallization from water brought the melting point up to 271-272.5°. In all m.p. determinations the sample darkens slightly a few degrees before melting, and melts to a red liquid. This material is believed to be the phosphate of 1-(homoveratrylamino)-6,7-dimethoxy-3,4-dihydroisoquinoline (LI).

Anal. Calcd. for $C_{21}H_{26}O_4N_2 \cdot H_3PO_4 \cdot 2H_2O$:

C, 49.97; H, 6.60; N, 5.55; P, 6.15; H_2O , 7.15.
(hydration)

Found:	50.35	6.57	6.37	5.84	8.7
	50.65	6.48	6.26	6.14	

The amidine itself separated out as a gum when the phosphate was added to dilute alkali, but difficulty was encountered in purifying it by recrystallization. Therefore a sample was prepared for analysis by first preparing a highly purified sample of the phosphate salt. Three and three-tenths grams of the 6.7 g. of once-crystallized phosphate (above) was recrystallized from 125 cc. of water with decolorizing charcoal, then from 80 cc. of water without charcoal. The wet precipitate was dissolved in 150 cc. of water, filtered, and made alkaline with sodium hydroxide. The solution immediately became cloudy.

After settling overnight the alkaline solution was decanted from a colorless gummy mass and extracted with two 75 cc. portions of ether. When the extracts were added to the beaker containing the gummy amidine, the latter appeared to dissolve readily upon stirring, but soon portions of the gum began to solidify and settle out as a powdery white precipitate. When the ether solution was diluted to 250 cc. and boiled, little of the white solid appeared to dissolve. The precipitate was filtered, dried, washed with water, and air-dried again. The product weighed 0.4 g., and melted at $134.2\text{--}134.8^{\circ}$, as compared to earlier samples melting in the range of 126 to 132° .

Evaporation of the ether mother liquors left a clear, colorless liquid. When this was covered with 30 cc. of ether, seeded with a crystal of the above 134° melting product and

stirred, it slowly solidified, producing another 0.6 g. of LI, m.p. 134.4-135.2°. This second crop was used for analysis.

Anal. Calcd. for $C_{21}H_{26}O_4N_2$: C, 68.07; H, 7.08; N, 7.56

Found: 67.51 6.92 7.75

b. Attempted hydrolysis of 1-(homoveratrylamino)-6,7-dimethoxy-3,4-dihydroisoquinoline (LI).

One gram of the phosphate salt was boiled in 30 cc. of 10% sodium hydroxide solution for two hours. A light tan, gummy layer separated soon after heating started, and remained in large, viscous droplets throughout the boiling period. After cooling, the alkaline solution was decanted and the gum washed with water. While standing overnight the gum slowly crystallized to a solid, nearly white, m.p. 129-132°. This crude sample of the amidine weighed 0.3 g., which represents a 40% recovery of starting material, but no other products were recovered by extracting the alkaline solution with ether.

c. Ring-closure experiments with s-bis-(β -phenethyl)-urea.

(a) One gram of s-bis-(β -phenethyl)-urea and 3 cc. phosphorous oxychloride were gently refluxed for one hour. Distillation of the phosphorous oxychloride under vacuum left a dark viscous residue, which did not appreciably dissolve in 100 ml. of boiling 2% hydrochloric acid. Nearly 0.5 g. of starting material was recovered by recrystallizing the residue

with ethanol. No additional crystalline products were obtained from the dark red viscous residue.

(b) Two grams of s-bis-(β -phenethyl)-urea, 4 cc. phosphorous oxychloride and 25 cc. toluene were gently refluxed for 4 hours, but most of the starting materials were again recovered after the toluene and phosphorous oxychloride had been evaporated.

(c) 1-(β -phenethylamino)-3,4-dihydroisoquinoline.

Six grams of s-bis-(β -phenethyl)-urea and 15 g. phosphorous pentoxide were refluxed in 100 cc. xylene for 4 hours. After cooling, the xylene layer was decanted, and the residue washed thoroughly with water, leaving 5 g. of dark, viscous liquid. The addition of 20 cc. ethanol caused 0.9 g. of light-colored solid to settle out slowly, m.p. 237-240°. In appearance and behavior this substance is similar to the phosphate of 1-(homoveratrylamino)-6,7-dimethoxy-3,4-dihydroisoquinoline, and there is about the same melting point difference as is common for β -phenethyl and homoveratryl derivatives, but no attempt was made to characterize the material.

C. Synthesis of Corydaldine Derivatives

a. N-Benzoylcorydaldine (XVIII).

Five-tenths gram of the phosphate salt of 1-(homover-atrylamino)-6,7-dimethoxy-3,4-dihydroisoquinoline was shaken with 1.0 cc. of benzoyl chloride in 5 cc. of distilled water, to which was gradually added 10 cc. of 10% sodium hydroxide solution in small portions. A moderate amount of heat was given off during the shaking, accompanied by formation of a light tan gum. The latter was washed with water and crystallized from 50% ethanol, producing 0.1 g. of colorless crystals, melting at 190-194°. Recrystallization from methanol yielded about 30 mg. of colorless granular crystals, m.p. 194-195°. Similar results were obtained when the amidine itself was used in place of its phosphate. Karrer, Eugster, and Ruttner (6) reported a melting point of 195-196° for their N-benzoylcorydaldine obtained from oxidation of N-benzoyl O-methylpsychotrine.

Anal. Calcd. for $C_{18}H_{17}O_4N$: C, 69.44; H, 5.51; N, 4.50

Found: 69.23 5.20 4.66

b. N-benzenesulfonylcorydaldine (LII).

Three-tenths gram of the phosphate salt of 1-(homover-atrylamino)-6,7-dimethoxy-3,4-dihydroisoquinoline was shaken with 0.5 cc. of benzenesulfonyl chloride in 5 cc. of 10% sodium hydroxide solution. Results were similar to those

obtained with benzoyl chloride, heat being evolved and a yellow gum forming. After cooling several hours, the gum, which had solidified, was washed with water and crystallized from ethanol. The yield was about 0.1 g., m.p. 191-192.5°. Two recrystallizations from 80% ethanol produced tiny, white crystals melting at 193.4-194.8°. This material is believed to be N-benzenesulfonylcorydaldine.

Anal. Calcd. for

$C_{17}H_{17}O_6NS$: C, 58.77; H, 4.93; N, 4.03; S, 9.02

Found:	58.96	4.81	4.36	10.04
	58.73	5.15	4.99	9.90

D. Preparation of Ethyl β -Acetonylglutarate.

a. Reduction of ethyl acetonedicarboxylate to ethyl β -hydroxyglutarate.

Two hundred fifty-two and five-tenths grams (1.25 mole) of ethyl acetonedicarboxylate was reduced in 5 batches of 50.5 g. (0.25 mole) each, in a Parr apparatus at room temperature, and under a hydrogen pressure of 35 to 45 lb./sq. in. The amount of platinum oxide catalyst per run varied from 0.35 to 0.50 g., with hydrogenation times of 7 to 12 hours. Within experimental accuracy, 0.25 mole of hydrogen was absorbed by each batch. About 150 cc. of absolute ethanol was used as the solvent for each run.

After removal of spent catalyst the combined ethanol solutions were distilled at atmospheric pressure until most of the ethanol had been removed, then under a pressure of 25 mm. on the steam bath. The residue was subjected to fractional distillation at 3.5 mm.; after a one cc. forerun, 235 g. (92%) of ethyl β -hydroxyglutarate was collected at 118-130°. The rise in temperature toward the end of distillation was believed to be due to superheating. A previous reduction product, prepared on a smaller scale, was subjected to more careful distillation, and most of the distillate came over at 117.5-118.0° (3.5 mm.). Interpolation of available literature data indicated a boiling point of 115-120° for the hydroxy ester and 112-115° for the keto ester at this pressure.

The refractive index of the fraction of b.p._{3.5} 117.5-118.0° was 1.4382 at 18°, but this does not differentiate between the hydroxy ester (1.4381 at 20°) and the keto ester (1.4378 at 24°). However, the quantitative absorption of hydrogen and the boiling point, leave little doubt as to the identity of the major portion of the distillate.

b. Formation of ethyl β -chloroglutarate from ethyl β -hydroxyglutarate. (41)

Two hundred fifteen grams (1.03 mole) of phosphorous pentachloride was placed in a 3-liter three-neck flask fitted with a reflux condensor, and then covered with one liter of dry ether. To this was added from a dropping funnel, 204 g. (1.00 mole) of ethyl β -hydroxyglutarate, at such a rate that gentle reflux was maintained. The escape of hydrogen chloride from the top of the condensor was noted. Previous small-scale runs showed the necessity of bringing the ether to reflux as soon as a small amount of ester was added, since reaction is very slow in cold ether. When the hydroxy ester was added too rapidly to cold ether, the reaction suddenly accelerated and excessive frothing caused loss of some material from the top of the reflux condenser. (According to the method described in the reference, where smaller quantities were employed, phosphorous pentachloride was added to the ester in ether solution, but an earlier preparation showed this method to be more hazardous and difficult to control.)

When all except about 5 g. of the phosphorøus penta-chloride had dissolved, the reaction ceased. This was expected since a slight excess of phosphorøus pentachloride was employed, and the phosphorøus oxychloride formed by the reaction is soluble in ether. The ether solution was then poured over 500 g. of water containing 500 g. of ice, and the mixture stirred until the ice was entirely melted. The two resulting layers were separated, the aqueous layer extracted several times with ether, and the combined ether solutions washed with 10% sodium carbonate solution until neutral, then washed with water. After drying over sodium sulfate, the ether was distilled on a steam-bath, first at atmospheric pressure and then down to 90 mm. A residue of 179 g. (81%) of light yellow liquid remained. No attempt was made to purify or analyze this material, other than to hydrolyze an aliquot and test for the chloride ion.

c. Condensation of ethyl β -chloroglutarate with ethyl acetoacetate to form ethyl ω -acetylmethanetriacetate (LV)(41).

The sodium salt of ethyl acetoacetate was prepared by dissolving 18.6 g. (0.81 mole) of sodium in 300 cc. of absolute ethanol, and reacting this solution with 116 g. (0.89 mole) of ethyl acetoacetate. To this was added the 179 g. (0.81 mole) of crude ethyl β -chloroglutarate (above), and the contents thoroughly mixed by swirling. Sodium chloride began to precipitate immediately. The reaction mixture was refluxed

on a steam-bath for 3 hours, with intermittent swirling.

The entire product including salt was added to 600 cc. of water and 40 cc. of concentrated hydrochloric acid. About 250 cc. of yellow liquid was separated from the aqueous layer, and the latter extracted with two 250 cc. portions of ether. The ether solutions were combined with the yellow liquid and washed with water. Distillation of the ether solution, the last part at 20 mm., on a steam-bath yielded 253 g. yellow liquid residue. If this were pure ethyl ω -acetylmethanetriacetate, it would represent a yield of 99%, based upon ethyl β -chloroglutarate, but it undoubtedly contains some ethyl acetoacetate, and possibly other by-products. No attempt was made to purify this crude product.

d. Decarboxylation and hydrolysis of ethyl ω -acetylmethanetriacetate to β -acetonylglutaric acid.

The procedure employed was the same as that used by Bently and Perkin (42) in decarboxylating ethyl α -acetylglutarate to γ -acetylbutyric acid.

A three-neck flask was fitted with a mercury seal stirrer and a condenser; to the top of the condenser was fitted a rubber tube for measuring carbon dioxide evolution (displacement of water). Into the flasks were placed the 253 g. of crude ester, 670 cc. of water, and 330 cc. of concentrated hydrochloric acid. Upon heating, gas evolution began at about 80° flask temperature and proceeded rapidly

at first, then steadily decreased until it practically ceased after 5 hours. Integration of the rate data indicated about 110% decarboxylation based upon crude ester, or nearly 100% based on the quantity of ethyl acetoacetate employed in the original condensation. During decarboxylation the immiscible liquid slowly disappeared, leaving a homogenous aqueous solution.

The acidic solution was saturated with ammonium sulfate and extracted with four 300 ml. portions of ether, and then the combined ether solution was extracted with two 200 ml. portions of 5N sodium hydroxide solution. The ether solution was dried over sodium sulfate and the ether distilled, leaving about 5 g. of a yellow liquid, which was discarded. The aqueous sodium hydroxide solution was re-acidified with hydrochloric acid, saturated with ammonium sulfate, and extracted with four 300 ml. portions of ether. The latter yielded 63 g. of syrupy liquid assumed to be β -acetylglutaric acid. In order to recover more product, both the original acidic reaction product and the acidified alkaline extract were extracted with about fifteen 200 ml. portions of ether, yielding another 34 g. of crude β -acetylglutaric acid. A continuous extraction would have been more efficient, but apparatus available at that time was not designed for handling this particular extraction.

Both batches of crude acid were dissolved in chloroform, causing a white solid to separate, 3.5 g. from each solution.

The combined chloroform solution (one liter) was allowed to stand in a stoppered flask several weeks, during which time another 0.5 g. of white solid settled out. Thus, the yield of crude β -acetonylglutaric acid was about 90 g., which is equivalent to a 60% yield based upon crude ethyl ω -acetyl-methanetriacetate, or 48% for the three successive reactions starting with pure ethyl β -hydroxyglutarate. The yield could probably have been slightly increased by more efficient extraction of the aqueous solutions. The nature of the solid by-product is discussed in a later section.

The crude β -acetonylglutaric acid is very soluble in water, ethanol, acetone, ether, and chloroform, and slightly soluble in benzene. It was kept in a chloroform solution of known concentration and measured portions of this were evaporated for use in the tests described below, as well as for its esterification.

e. Identification tests with β -acetonylglutaric acid.

(a) Melting point. It is very difficult to crystallize this acid, but in an earlier preparation a little solid melting at about $60-70^{\circ}$ was obtained by letting a benzene solution slowly evaporate for several days. It was apparently hygroscopic and formed a solution upon being exposed to the air for a few minutes. Attempts to obtain more of these crystals were unsuccessful.

(b) Neutralization equivalent. The above solid possessed a N.E. of 99 ± 5 (theoretical is 94).

(c) Analysis. The acid itself was not purified for analysis, but its ethyl ester (described later) gave very close to theoretical values when analyzed for carbon and hydrogen.

(d) Treatment with acetic anhydride, for the purpose of obtaining an anhydride or lactol gave a trace of solid melting at $171-172.5^{\circ}$, but this was not identified due to the small yield.

(e) Iodoform test--positive.

(f) Oxime derivative--unsuccessful.

(g) Semicarbazone derivative--unsuccessful.

(h) 2,4-dinitrophenylhydrazone derivative--after several days a dark-red oil resulted, which could not be crystallized.

(i) Attempts were made to prepare a simple diamide by reacting with phosphorous pentachloride and then with aqueous ammonia, but apparently the ammonium salt of the acid was recovered.

f. Preparation of ethyl β -acetylglutarate (LVI).

The procedure employed was that described in Organic Syntheses (43) for the esterification of adipic acid.

Twenty-eight and two-tenths grams (0.150 mole) of β -acetylglutaric acid was dissolved in 59 cc. (1.00 mole) of absolute ethanol containing 27 cc. of toluene and 15 drops

of concentrated sulfuric acid. A downward condenser was connected and distillation maintained (electric mantle) at about 25 drops per minute, the distillate being collected over 25 g. of potassium carbonate. While 50 cc. of distillate was coming over, the thermometer gradually rose from 75 to 78°. The distillate was filtered back into the reaction flask and the process repeated; this time a b.p. of 78° was reached after about 20 cc. had come over. Distillation was continued, the final stages being carried out at 30 mm. on a steam-bath.

The residue was dissolved in 300 cc. of ether, washed with 10% sodium carbonate solution, and dried over sodium sulfate. After distillation of the ether, the last part in vacuo, on a steam-bath, 21 g. of residue (57% crude yield) remained. This was fractionally distilled, yielding 13 g. (36%) boiling at 139-140° (3.5 mm.). The low yield was believed due to incomplete esterification, so the sodium carbonate washings were acidified and extracted with ether, but only 1.0 g. of acidic liquid was recovered in this way. The low yield thus remains unexplained.

g. Identification tests with ethyl β -acetylglutarate.

(a) Analysis. A "heart-cut" of the 139-140° (3.5 mm.) fraction was used for analytical purposes.

Anal. Calcd. for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25

Found: 59.30 8.11

(b) Iodoform test--positive.

(c) 2,4-dinitrophenylhydrazone derivative--formed a dark-red liquid which could not be crystallized.

(d) Semicarbazone derivative--unsuccessful.

h. By-product obtained in the hydrolysis and decarboxylation of ethyl ω -acetylmethanetriacetate (p. 63).

The 7.5 g. of white solid acid which separated from the chloroform solution of the crude β -acetylglutaric acid was found to be very slightly soluble in ether, and a small amount was recrystallized from ether, m.p. 194-198° (with decomp.). It gave a positive iodoform test, and, on the basis of analysis, was thought to be un-decarboxylated ω -acetylmethanetriacetic acid.

Anal. Calcd. for $C_9H_{10}O_7$: C, 46.53; H, 5.21

Found:	47.07	4.92 ₀
	47.00	5.03

However, the neutralization equivalent was 68[±] 1, while the theoretical value for ω -acetylmethanetriacetic acid is 77.

E. Reaction of β -Acetonylglutaric Acid and its Ester with Homoveratrylamine and β -Phenethylamine.

The general method employed by Child and Pyman (29), Hahn and Gudjohns (30), and King and Robinson (31), was used in the first attempted condensations, with variations in the procedure being used in later experiments. A great number of reactions were carried out in attempting, first, to obtain a diamide, and then to improve the yield. Only those attempts which proved somewhat successful will be described in any detail.

For most of the early runs an amine:ester ratio of 3:1 was employed, due to the possibility of Schiff base formation. The reactants were mixed in a small flask and heated without stirring in an oil-bath. During the first tests the flask was open to the atmosphere, but in later runs it was protected by a calcium chloride-soda lime tube. This was done for the purposes of keeping out carbon dioxide, which forms homoveratrylamine carbonate on the sides of the flask, and of providing for the attachment of a water-pump vacuum line.

In searching for crystallizable reaction products two general methods were employed: (1) The reaction product was dissolved in ether or benzene, then extracted with dilute mineral acid and base, followed by investigation of the three solutions. (2) The method which proved most successful was to add all the reaction product to dilute hydrochloric acid

and let the mixture stand for several hours to several days. A precipitate slowly formed in a few cases.

The reactions are summarized below (usually a total of about 2 or 3 g. of reactants was employed).

a. Homoveratrylamine and β -acetylglutaric acid.

(a) 3:1 ratio, 2 hrs., 150-160°, only tarry products.

(b) " " 170-180°, "

(c) " " 200-210°, "

(d) " " 230-240°, "

In all of the above reactions, there was evolution of vapor, at least part of it water.

b. Homoveratrylamine and ethyl β -acetylglutarate.

(a) 3:1 ratio, 2 hrs., 160-180°, only tarry products.

(b) " 1 hr., 120°, apparently no reaction.

(c) " " 145-150°, some reaction, but

no crystallizable product.

(d) 3:1 ratio, 2 hrs., 155-165°, only tarry products.

(e) " 1 hr., 100°, in a flask protected by

a calcium chloride-soda lime tube. There was no apparent reaction, nor was there any when the same reactants were heated another 4 hours at 100°.

(f) 3:1, 130°, 4 hours, in a flask protected by a drying tube, and under a pressure of 15 mm. Boiling during the early stages of the reaction gradually diminished, but no crystalline products were obtained.

(g) 3:1, 1 hr., 185-200°, low pressure, only tarry residues.

(h) 3:1, 1 hr., 200-220°, low pressure, only tarry residues.

(i) 2:1, refluxed in xylene (140°) for one hour.

Distillation of the xylene left a residue still containing a large amount of unchanged homoveratrylamine.

(j) 3:1, refluxed in mesitylene (160°) for one hour.

Distillation of the mesitylene left a dark oily residue containing a trace of solid. The amount was too small even for a melting point determination.

(k) Following the successful formation of N,N'-di-(β -phenethyl)- β -acetylglutaramide (page 73), the successful method of high amine:ester ratio was also tried with homoveratrylamine.

One and one-hundredth grams of ethyl β -acetylglutamate was dissolved in 15 cc. of freshly-distilled homoveratrylamine (1:20) in a 100 cc. flask protected by a drying tube, and the flask was heated in an oil-bath at 120-125° for three hours. After cooling, about 10 drops of the light yellow liquid reactant were added to dilute hydrochloric acid; they dissolved immediately, and the solution produced no precipitate after standing overnight.

The reactants were then heated for 3 more hours, this time at 130-135°. Since addition of 5 drops of the product to dilute hydrochloric acid caused formation of a light-colored

scum, the flask was subjected to a third heating of 2 hours, at 135-145°. This time, after testing a few drops in dilute acid, about 1/3 of the reaction mixture was added to 50 cc. of dilute hydrochloric acid. The total amount of tan precipitate which formed was quite small, so the rest of the reaction mixture was heated a 4th time for 2 1/2 hours at 145-150°. Again 1/3 of the remaining product was added to 50 cc. of dilute acid, but the yield of precipitate appeared no greater than in the previous case. Therefore the reaction mixture was heated yet another 3 hours at 150-155°. After this heating the rest of the material in the flask was added to 75 cc. of 2% hydrochloric acid, and in a few hours a gummy precipitate settled out. The acid solution was decanted, neutralized with sodium hydroxide solution, then made slightly acidic, causing some more of the brown gum to settle out. Both batches of brown residue were rinsed with water, dissolved in acetone, combined, and the acetone evaporated.

To the residue was added 250 cc. of ligroin, and after heating on a steam-bath for one hour, the resulting yellow solution was filtered and left at room temperature overnight. The precipitate which settled out was filtered and air-dried, yielding 80 mg. of a tan, powdery solid. This material melted to a red liquid at 60-80°. Attempts to obtain a truly crystalline solid from this and other portions of the resinous material were unsuccessful. On the basis of comparison with other di-homoveratrylamides and di-(β -

phenethyl)-amides, the desired product should have a melting point in the neighborhood of 150° .

c. β -Phenethylamine and β -acetonylglutaric acid.

(a) 3:1, $150-170^{\circ}$, 1.5 hr., 25 mm. After dissolving the reaction product in dilute hydrochloric acid a small amount of white solid settled out after several days. This was separated from the mass of gummy residue by several recrystallizations (with charcoal treatment) from acetone-carbon tetrachloride solution. (The substance is soluble in acetone, slightly soluble in carbon tetrachloride.) Finally, about 18 mg. (1% yield) of a white solid, m.p. $152-156^{\circ}$, was obtained. This was not further investigated but is probably the same material obtained with ethyl β -acetonylglutarate (below).

d. β -phenethylamine and ethyl β -acetonylglutarate.

(a) One gram of ester and 1.5 g. of amine (1:3 molar ratio) were heated for 2 hours at $150-160^{\circ}$, under a pressure of 25 mm. After cooling, the product was still fluid and possessed an amine-like odor. The entire reaction product was shaken with 50 cc. of 3% hydrochloric acid and two 50 cc. portions of ether. A small amount of gummy residue remained undissolved, and was left in the aqueous layer. Evaporation of the ether layer left about 50 mg. of residue containing a few crystalline particles. Treatment with a little acetone liberated about 25 mg. of light tan solid. Meanwhile, the

aqueous solution, after standing a few hours, had produced a fluffy white precipitate mixed with a gummy residue. The mixed residue was dissolved in ethanol, treated with charcoal, and re-precipitated by adding water and evaporating the ethanol. This yielded 35 mg. of buff-colored solid. After standing another day the aqueous hydrochloric acid filtrate had precipitated another 10 mg. of white fluffy material, which melted at 145-149°.

The three portions of solid obtained above (75 mg. or about 5% yield) were combined and recrystallized twice (with charcoal) from ethanol-carbon tetrachloride solution (about 10% ethanol), yielding 10 mg. of white powdery solid, m.p. 170.6-1.4°.

Anal. Calcd. for $C_{24}H_{30}O_3N_2$: C, 73.06; H, 7.67; N, 7.10

Found: 72.10 7.62 6.22

(b) One and three-tenths grams of ester and 2.6 g. of amine (1:4 molar ratio) were heated for 3 hours at 120-140° at 25 mm. This time the entire reaction product was added to 50 cc. of 3% hydrochloric acid. After several hours the dark red fluid had changed to a gummy grey precipitate. Three recrystallizations (with charcoal) of the latter from carbon tetrachloride-ethanol produced 27 mg. of white solid melting at 155-158° (about 100 mg. of this material was estimated to be originally present). Two more recrystallizations yielded about 6 mg., m.p. 169.2-170°.

All of the mother liquors from the recrystallizations

of both of the above reaction products were combined and evaporated to dryness. The residue was recrystallized 3 times from carbon tetrachloride containing 5-10% acetone, yielding 20 mg. of a white material melting at 151-153°.

Anal. Calcd. for $C_{24}H_{30}O_3N_2$: C, 73.06; H, 7.67; N, 7.10

Found: 73.33 7.88 7.60

(c) Several other small-scale condensations at various temperatures and reaction times failed to improve upon the yield of the 151-153° melting product, but by fractionally distilling the commercial stock of β -phenethylamine before condensation with the ester, and using the middle cut, no more of the 170° melting product was obtained. In view of the analytical results, the 151-153° product will be considered to be N,N'-di(β -phenethyl)- β -acetylglutaramide (LVII, with hydrogens in place of the methoxyl groups).

Additional small scale condensations showed that the yield of diamide could be improved by increasing the amine to ester ratio. The largest scale reaction will be described.

(d) Five grams (0.0215 mole) of the ester was dissolved in 50.0 g. (0.415 mole) of the freshly distilled amine in a 100 cc. flask, connected via an ice-trap to a water-pump. The flask was heated in an oil-bath at 135-145° for one-half hour at 100 mm., then for one hour at 145-155° and 200 mm. The trap in the vacuum line had only caught a few drops of liquid, so the flask was heated 1 1/2 hours at 150-155°. Addition of 10 drops of the reaction mixture to dilute

hydrochloric acid failed to produce an appreciable precipitate, so heating was continued another two hours at 145-155°.

The resulting clear red liquid was added to 300 cc. of water, and concentrated hydrochloric acid was added to the mixture until it was just acid to litmus. Then an excess of 5 cc. of acid was added. After 3 days a mixture of white granular precipitate and tan amorphous solid which had formed was removed by filtration. After washing and air-drying, this product was ground in a mortar under 8 successive 20-25 cc. portions of ether. Each ether solution was decanted, along with a portion of suspended light-colored solid; the solutions became increasingly lighter, going from dark brown to light yellow. When all the solids had been decanted in this way, they were collected on a filter, washed with a little more ether, then air-dried, yielding 1.48 g. of light buff-colored solid. Evaporation of the ether filtrates yielded about 2 g. of a dark tarry liquid.

The acidic filtrate was made neutral with sodium hydroxide solution and then just barely acidic with hydrochloric acid. After several days this solution produced another 0.32 g. of light tan solid. The total yield of 1.8 g. of solid material represents 23% of the theoretical yield based upon ethyl β -acetylglutarate.

f. Ring-closure experiments with N,N'-di(β -phenethyl)- β -acetylglutaramide.

Eight-tenths gram of the crude diamide (above) was

added to 25 cc. of toluene and 3 cc. of phosphorous oxychloride, with no apparent reaction. The mixture was gently refluxed for one hour, considerable hydrogen chloride being evolved during the first half-hour. The toluene solution was decanted into a beaker of water and the mixture shaken to decompose the excess phosphorous oxychloride. The tarry residue in the original reaction flask was treated successively with four 70 cc. portions of 2% hydrochloric acid solution with warming on a steam-bath. Each of the acid solutions was made alkaline with sodium hydroxide solution, causing gummy precipitates to settle out slowly. Each mixture was filtered, and the washed and dried precipitates were dissolved in acetone. The acetone solutions were combined, and evaporation to dryness left about 0.2 g. of tan sticky solid which could not be crystallized. It was slightly soluble in water, forming a solution alkaline to phenolphthalein. The toluene solution (above) was also extracted with dilute acid, but, when made alkaline, this gave only a trace of precipitate.

The above tan solid and 0.3 g. of picric acid were dissolved in 20 cc. of ethanol, and the solution was gently boiled on a steam-bath for 30 minutes. After standing overnight, a little red liquid had settled out; it was solidified by decanting the ethanol solution and leaving the residue covered overnight with ligroin. The resulting amorphous solid was treated with 100 cc. of refluxing benzene for 4 hours, effecting solution of all but a little dark residue.

After standing several days a small crop of mustard-colored needles had formed; filtered, washed, and dried, they weighed 23 mg., m.p. 129-131°. Slow recrystallization from 20 cc. of benzene produced 17 mg., melting at 133.0-134.6°.

Anal. Calcd. for the monopicrate of s-bis-(3',4',-dihydro-1'-isoquinolyl)-2-acetonylpropane, $C_{30}H_{29}O_8N_5$:

C, 61.4; H, 4.97; N, 11.9

Calcd. for the dipicrate of s-bis-(3',4',-dihydro-1'-isoquinolyl)-2-acetonylpropane, $C_{36}H_{32}O_{14}N_8$:

C, 54.0; H, 4.03; N, 14.0

Found: C, 64.5; H, 5.97; N, 11.7

Attempts to prepare more of the 134° melting picrate from the mother liquors yielded only liquids and amorphous solids.

(b) Essentially the same procedure was followed with 1.01 g. of pure N,N'-di(β -phenethyl)- β -acetonylglutaramide. This also formed a red liquid picrate, but all attempts to obtain more of the 134° melting picrate by crystallization from benzene were unsuccessful. It could not be crystallized from water or from ethanol. Finally, evaporation of a benzene solution left a mustard-yellow crystalline residue, which melted at about 150° after beginning to soften at about 125°. However, not enough of this could be obtained for purposes of characterization.

F. Attempted Synthesis Based upon Diethyl Ethylmalonate.

a. Condensation between the sodium salt of diethyl ethylmalonate and ethyl β -chloroglutarate.

Fifteen small pieces of sodium weighing 6.0 g. (0.26 mole) were added to 400 cc. of dry ether in a 3-liter flask fitted with a reflux condenser and dropping funnel. From the funnel was slowly added 47.0 g. (0.25 mole) of freshly-distilled diethyl ethylmalonate. A fairly rapid exothermic reaction occurred, but ebullition was not excessive. Most of the sodium dissolved in 30 minutes.

While the sodium was reacting, ethyl β -chloroglutarate was prepared from 53 g. (0.255 mole) of phosphorous pentachloride and 51.0 g. (0.25 mole) of ethyl β -hydroxyglutarate according to the method previously described (p. 59). The washed ether solution of ethyl β -chloroglutarate was left drying over sodium sulfate while the sodium finished reacting.

After three hours, all but about 0.1 g. of the sodium had dissolved, so the ether solution of ethyl β -chloroglutarate was filtered into the suspension of the sodium salt. This caused the ether solution to become cloudy immediately. Finely-divided sodium chloride precipitated quite rapidly, but the mixture was gently refluxed for 10 hours on a steam-bath.

The entire contents were transferred to a separatory funnel, made acidic by the addition of 2 drops of glacial

acetic acid, and washed with three 35 cc. portions and then three 20 cc. portions of water. The first two washings removed all the solid material present and most of the yellow color from the ether, but the washings remained yellow until the final one, which was light straw colored. The ether solution was evaporated, leaving 75 cc. of light yellow liquid.

b. β -(1,1-dicarboxypropyl)-glutaric acid (LXII).

To the 75 cc. of crude ester, still containing a little ether, were added 84 g. (1.5 moles) of potassium hydroxide and 85 cc. of water. As the potassium hydroxide was stirred into the solution the last of the ether evaporated, leaving a light yellow lower aqueous layer and a light orange upper layer. The mixture was heated slowly in an open flask until it reached about 70°, whereupon a rather vigorous reaction occurred, and the solution rapidly became nearly homogeneous (still a little cloudy). The product was then boiled for 2 hours, during which time the temperature rose from 80° to 112°, thus ensuring quite complete removal of ethanol.

The deep red alkaline solution was diluted to 200 cc. and extracted with 75 cc., then 50 cc. of ether. The washed solution, still red, was acidified with 50 cc. of concentrated sulfuric acid (1.8 equiv.). Upon cooling, a large amount of crystals, presumably potassium sulfate, separated. The saturated aqueous solution was extracted with three 200 cc. portions of ether, which were dried and evaporated separately.

The acid solution was then treated with ether in a continuous extraction apparatus. With an ether circulation rate of approximately 10 to 20 cc./minute, four extractions of about 20 to 25 hours each, were made. The last one yielded practically nothing.

A great number of crystallizations were carried out with the products obtained from these extractions, ultimately yielding three substances. On the basis of only slight solubility in ether, 10.5 g. of a white solid melting with decomposition at 204-206°, was separated from the extraction fractions. Since the 4th continuous extraction yielded less than 1/20 as much of this as the three previous ones, it was assumed that extraction was quite complete. This material is believed to be the desired product, β -(1,1-dicarboxypropyl)-glutaric acid (LXII), and represents a yield of only 16%.

Anal. Calcd. for $C_{10}H_{14}O_8$: C, 45.78; H, 5.38

Found:	45.73	4.71
	46.67	5.01
	46.76	4.70

Although the analytical results are not as close as might be desired, the neutralization equivalent was determined to be 66 ± 1 (theoret., 65.5).

The second substance separated from the ether extractions was 12.5 g. (38% recovery) of ethyl malonic acid, m.p. 110-113° (lit., 111.5°). This acid, quite soluble in ether, was obtained only from the three batch extracts, and crystallized from benzene. It possessed a neutralization equivalent

of 66 ± 1 (theor., 66), and was readily decarboxylated at $150-160^\circ$ to a liquid smelling like butyric acid, and giving a neutralization equivalent of 89 ± 1 (theoret., 88).

After separation of the two solid acids, about 15 g. of yellow syrupy liquid remained, most of it originally from the first batch ether extract. This substance dissolved readily in water and gave a neutralization equivalent of approximately 100, but no effort was made to identify it. It possessed a slight butyric acid odor, but this is undoubtedly a minor constituent.

c. Decarboxylation experiments with β -(1,1-dicarboxypropyl)-glutaric acid.

(a) Acid-catalyzed decarboxylation.

When 3.0 g. of the tetracarboxylic acid was gently refluxed in 30 cc. of 3N hydrochloric acid, carbon dioxide was slowly evolved, but after 30 minutes, with less than 25% of the theoretical quantity of gas collected, the decarboxylation ceased. The acid solution was saturated with ammonium sulfate and extracted with three 100 cc. portions of ether. From the ether were recovered 1.4 g. of the tetracarboxylic acid, and 0.3 g. of a brown gummy substance, possessing a neutralization equivalent of 92 ± 2 . The expected decarboxylation product, β -(1-carboxypropyl)-glutaric acid (LXIII), would possess a neutralization equivalent of 73, and should be a crystalline substance.

(b) Thermal decarboxylation.

About 1 g. of the tetracarboxylic acid was placed in a test tube fitted with a tube for bubbling evolved gases through calcium hydroxide solution. When the test tube was heated in an oil-bath, carbon dioxide evolution started slowly between 180° and 190° , and became very rapid above 200° . After 10 minutes at $200-210^{\circ}$, the bubbling rate slowed down. When it settled to a slow steady evolution, the test tube was removed from the oil-bath. The product was a red syrup which was soluble in water and gave a neutralization equivalent of 97 ± 2 . It could not be crystallized.

Another 1 g. sample was placed in a weighing bottle and heated in an oven at 180° . Every 1 1/2 hour the bottle was weighed and a small portion removed for a neutralization equivalent determination. During the first few hours it gradually changed from a white powder to a reddish-brown porous resin, plastic when hot but brittle when cold. During the first 6 hours it decomposed at the rate of about 4% by weight per hour, but after 6 hours the rate decreased to less than 1% per hour. Parallel with this, the neutralization equivalent increased steadily from 66 to 100 ± 3 , and retained this value until after heating was discontinued at 10 1/2 hours. The total weight lost after 6 hours was 23%.

BIBLIOGRAPHY

1. Pelletier and Magendie, Ann. Chim. Phys., 4, 172 (1817).
2. Paul and Cownley, Pharm. J., 25, 111 (1894).
3. Pyman, J. Chem. Soc., 111, 419 (1917).
4. Pailer and Porschinski, Monatsh., 80, 94 (1949).
5. Evstigneeva, et al, Doklady Akad. Nauk. S.S.S.R., 75, No. 4, 539 (1950).
6. Karrer, Eugster, and Ruttner, Helv. Chim. Acta, 31, 1219 (1948).
7. Carr and Pyman, J. Chem. Soc., 105, 1591 (1914).
8. Hammerslag, "The Technology and Chemistry of Alkaloids," D. Van Nostrand, New York, 1950, p. 157.
9. Keller, Arch. Pharm., 249, 512 (1911).
10. Keller, Arch. Pharm., 251, 701 (1913).
11. Windaus and Hermanns, Ber., 47, 1470 (1914).
12. Karrer, Ber., 49, 2057 (1916).
13. Carr and Pyman, Proc. Chem. Soc., 29, 226 (1913).
14. Pyman, J. Chem. Soc., 113, 222 (1918).
15. Brindley and Pyman, J. Chem. Soc., 1927, 1067.
16. Spaeth and Leithe, Ber., 60, 688 (1927).
17. Ahl and Reichstein, Helv. Chim. Acta, 27, 366 (1944).
18. Staub, Helv. Chim. Acta, 10, 826 (1927).
19. Spaeth and Pailer, Monatsh., 78, 348 (1948).
20. Pailer, Monatsh., 79, 127 (1948).
21. Pailer, Monatsh., 79, 331 (1948).
22. Battersby and Openshaw, J. Chem. Soc., 1949, 3207.

23. Pailer and Porschinski, Monatsh., 80, 101 (1949).
24. Moyer and McEwen, J. Am. Chem. Soc., 73, 3075 (1951).
25. Sugasawa and Kobayashi, J. Pharm. Soc. Japan, 69, 85 (1949).
26. Sugasawa and Kobayashi, J. Pharm. Soc. Japan, 69, 88 (1949).
27. Kobayashi, J. Pharm. Soc., Japan, 69, 91 (1949).
28. Battersby and Openshaw, Experientia, 6, 378 (1950).
29. Child and Pyman, J. Chem. Soc., 1929, 2010.
30. Hahn and Gudjons, Ber. 71, 2183 (1938).
31. King and Robinson, J. Chem. Soc., 1938, 2119.
32. Besthorn and Garben, Ber., 33, 3439 (1900).
33. Naik and Thosar, J. Ind. Chem. Soc., 9, 127 (1932).
34. Mohunta and Ray, J. Chem. Soc., 1934, 1263.
35. Curtius and Jordan, J. Prakt. Chem., 64, 297 (1901).
36. Thiele and Pickard, Ann., 309, 189 (1899).
37. Weerman and Jongkees, Rec. Trav. Chim., 25, 238 (1906).
38. Roberts and Edwards, J. Am. Chem. Soc., 72, 5537 (1950).
39. Shriner and Neumann, Chem. Rev., 35, 351 (1944).
40. Barber, J. Chem. Soc., 1943, 101.
41. Dreifuss and Ingold, J. Chem. Soc., 123, 2964 (1923).
42. Bentley and Perkin, J. Chem. Soc., 69, 1511 (1896).
43. Micovic, in "Organic Syntheses, Coll. Vol. II," A. H. Blatt, Editor-in-Chief, Wiley, New York, 1943, p. 264.